How is the adherence in community hospitals to national guidelines for the workup of non-palpable, screen detected breast lesions?

Voogd, A.C.; Broekman, J.M.; Crommelin, M.A.; van der Horst, F.; Razenberg, P.P.A.; Repelaer van Driel, O.J.; Roukema, Anne

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ABSTRACTS

8th Congress of the European Society of Surgical Oncology,
being held at University College, Dublin, on 4–7 September 1996

ACCEPTED ORAL PRESENTATIONS

Breast

1. CA15-3 and TPS are complementary tumour markers in breast cancer

National Breast Cancer Research Institute, Department of Surgery, University College Hospital, Galway, Ireland

Tumour markers are finding increased acceptance in the management of patients with breast carcinoma. No tumour marker is ideal and a combination may be of greater benefit. Markers should be chosen which measure different aspects of tumour cell function because many merely identify different epitope sites on the same molecule. In this study we have prospectively assessed aspects of tumour cell function because many merely identify different epitope sites on the same molecule. In this study we have prospectively assessed CA15-3 (a marker of tumour burden) and TPS (tissue polypeptide specific antigen, a marker of cell proliferation) in patients undergoing follow-up breast carcinoma, 60 of whom developed metastatic disease.

Table 1. Mean (SEM) tumour marker levels in different categories of disease:

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>TPS Mean (SEM)</th>
<th>CA15-3 Mean (SEM)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign disease (n=89)</td>
<td>51.6 (3.8)</td>
<td>21 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Prooperative (n=135)</td>
<td>95.2</td>
<td>30.6 (2.7)</td>
<td></td>
</tr>
<tr>
<td>No Rec (n=303)</td>
<td>63.7 (3.8)</td>
<td>21.8 (0.63)</td>
<td></td>
</tr>
<tr>
<td>Locoregional (n=30)</td>
<td>145.4 (37.6)</td>
<td>40.3 (7.6)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Bone Mets (n=41)</td>
<td>269.6 (52.2)</td>
<td>87.1 (12)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Visceral Mets (n=19)</td>
<td>660 (161)</td>
<td>151.9 (23.1)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

The sensitivity of these individual markers for the detection of locoregional recurrence was 45% (CA15-3) and 48% (TPS), and metastatic disease was 78% (CA15-3) and 83% (TPS). The combination improved sensitivity to 94% (locoregional disease) and 93% (metastases). These markers identify different aspects of tumour function, both of which may have prognostic significance and we recommend this combination of markers in breast carcinoma.

2. FGF-2: A new prognostic indicator in breast cancer?

C. Yangou1, Y. Luqmani2, R. C. Coope2, S. Shousha1, D. Simnett1, and R. C. Coste1
Departments of 1Surgery, 2Medical Oncology and 3Histopathology, Charing Cross Hospital, London, UK

FGF-2, a prototype member of the family of FGFs, is a potent angiogenic factor and is involved in cellular growth, differentiation and tumourigenesis. It has been detected in a variety of human cancers, including breast cancer, but has not been linked to prognosis or survival.

In this study, we have investigated the expression of FGF-2 protein in 30 normal and malignant breast tissues by Western blotting and immunohistochemistry and FGF-2 mRNA in 51 breast cancers using a PCR methodology. Levels of expression were correlated with clinicopathological parameters and survival.

FGF-2 protein was detected in all tissues, but staining of the malignant epithelial cells was seen in only 12 out of 20 IDCs, 3 out of 7 DCIS and none of the 3 ILCs. Normal breast epithelial cells obtained from tissue surrounding 15 carcinomas showed intense FGF-2 staining.

FGF-2 mRNA was detected in all cancers tested, but levels did not correlate with T-stage, nodal status and oestrogen receptor positivity. However, there was an association between higher levels of FGF-2 and improved survival (median follow-up 84 months). Univariate survival analyses showed that this reached statistical significance for both overall (P=0.040) and disease-free survival (P=0.022). Various confounding variables including nodal status did not have any effect on this association (Cox's proportional hazards model).

Our results show that FGF-2 is related to survival and may have some role as a prognostic indicator in breast cancer.

3. The use of CO2 laser for palliative surgery in advanced breast cancer

S. Gillet, I. Kaplan, I. Kott
Dept of Plastic Surgery B and Experimental Surgery, Felsenstein Medical Research Center, Rubin Medical Center (Beilinson Campus), Petah Tiqwa, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Since 1980, operations with the CO2 laser have been performed in our center in 22 women with advanced or neglected breast cancer, with recurrent breast cancer, or chest wall metastases of breast cancer. Such tumours may give rise to symptoms of hemorrhage, infection, sepsis, and especially, pain and discomfort. In our cases, the tumours were ulcerated or fungating, with infection, bleeding, and malodor which resulted in an intolerable problem for both partner and family. Cytotoxic drugs or radiation are generally ineffective in controlling the affected areas. Although surgery in such cases can only be palliative, it benefits the patients. CO2 laser has been found effective in sealing blood vessels and lymphatics, especially highly infective areas, and is associated with good healing and minimal post-operative pain and discomfort. Because of these advantages, we used the CO2 laser (beam, 20–40 watts) to excise the tumoral masses; primary suturing, split thickness skin grafts or rotation of local or distant flaps was applied to cover the defects. During surgery, there was a significant reduction in blood loss, good take of the skin grafts, fewer post-operative infective complications, no necrosis of flaps, little post-operative scarring, no post-operative wound dehiscence, and less post-operative pain. We recommend the use of the CO2 laser beam for palliative treatment of advanced breast cancer.

4. Efficacy of fibrin glue (Tisseel*) in axillary lymph node removal for breast cancer: prospective randomized trial

Dept Surgery, University of Lyon, CHLS, 69495 Pierre Benite cedex, France

From January 1993 to January 1994, a prospective randomized trial was conducted in our department to evaluate the efficacy of fibrin glue (Tisseel*) on lymphostasis in axillary lymph node removal for breast cancer.
Abstracts

Material and Methods: 108 patients (2 men, 106 women, mean age 60.1 years) with breast cancer were included in the study and operated on by the same two surgeons. Randomization was performed at the end of surgical lymph node dissection (axillary). Group 1 (n = 55, mean age 60.6 years) received 2 cc of fibrin glue (Tisseel®) with high thrombin concentration (500U/ml) and 3000 KIU/ml aprotinin: Group 2 (n = 53, mean age 62.5 years) received no fibrin glue. For both groups, a tubular drain was inserted in axillary dissection area for 6 days. Both groups were similar regarding cancer staging, tumor size, lymph node involvement and nodal yield.

Results: No mortality occurred. Immediate post-operative morbidity rates were the same in the 2 groups (0/50 vs 1/58, ns). Mean daily drainage in groups 1 and 2 were 65.3 cc vs 83.5 cc (P=0.03) on the first post-operative day, 55.1 cc vs 84.1 cc (P=0.01) on the second day, 48.3 cc vs 65.6 cc (P=0.01) on the third day, 28.5 cc vs 49.8 cc (P=0.01) on the fourth day, 28.5 cc vs 47.5 cc (P=0.04) on the fifth day and 24.2 cc vs 55.8 cc (P=0.01) on the sixth day. Mean total drainage was 214.4 cc in group 1 and 407.8 cc in group 2 (P=0.001). Mean hospital stay was 8.0 days in group 1 and 10.3 days in group 2 (P<0.05). Delayed complication rates were similar in both groups: one lymphocyst in group 1 and one lymphocyst in group 2 (ns).

Conclusion: Results of this trial confirmed the one of the preliminary randomized trial we performed 3 years ago. It appears that fibrin glue can be safely used in axillary lymph node removal. Fibrin glue improves postoperative lymphostasis (smaller drainage quantity). Shorter hospital stay even if our series shows no difference in the incidence of delayed lymphocyst.

5. Assessing the adequacy of mastectomy by flap biopsies
J. C. Dougherty, E. Mallon, S. Stallard, W. D. George
University Department of Surgery, Western Infirmary, Glasgow, UK

Local recurrence occurs in 2-5% of patients following mastectomy. This may occur many years after surgery even for small tumours. This suggests that local recurrence may not be completely explained by the presence of residual malignant cells at the time of mastectomy. Another possible explanation is that local recurrence could be due to new tumour growth arising from residual breast tissue left on the flap at the time of surgery.

The aim of this pilot study was to assess the adequacy of mastectomy in removing all breast tissue from the skin flaps at the time of surgery. A total of 31 patients with a preoperative tissue diagnosis of invasive breast cancer were studied. All mastectomies were performed or supervised by a consultant or senior registrar and once the flaps had been dissected two biopsies of the most prominent areas of the undersurface of the flaps were located by the assistant and sent to pathology to look for epithelial elements. The mean age of the patients was 57 (range 38-75) and mean tumour size of 28 mm (range 7-70). In six patients breast epithelium was present in the flap biopsies and this was operator independent.

We conclude that even when a deliberate attempt is made to cut thin flaps there is still a considerable risk of leaving residual breast tissue at the time of mastectomy and this may be a contributory factor in the development of local recurrence.

6. Prognostic significance of p53 protein accumulation in male breast cancer (MBC)
B. Maussdka, M. T. Ionta, G. Porcu, P. G. Cañé, P. Dessalvi, A. Tarquini
Institute of Surgical and Clinical Oncology and A. Buscini Cancer Hospital, 09100 Cagliari, Italy

p53 abnormalities are frequently (20-40%) reported in female breast cancer (FBC) and are often correlated with poor prognosis. Relatively few studies are concerned with its expression, mutation and correlation with prognosis in MBC. However, while some data (ASCO 1994, 1276) indicate that MBC may demonstrate p53 abnormalities in 20-40% of cases, others found that MBC rarely overexpresses p53 protein, others indicate that it is similar to the female counterpart. p53 abnormalities in MBC were studied for prognostic factors (size, nodes, grading, ER, PgR, Ki-67 L.I./PCNA) and in (21 pts) for monoclonal mouse and anti-human p53 antibodies (Dako, p53, D07) on formalin-fixed-embedded tissue sections. Staining was assessed by the number of cells and the intensity of the cells staining. Positivity was considered when >20% of cells stained. The median patient (pt) age was 65 years; there were 23 infiltrating ductal (79.3%), 2 lobular (10.3%), 2 tubular (6.9%) and 1 apocrine (3.4%); 17 (58.6%) pts have LN involvement. All pts underwent mastectomy (radical in 24 pts). Of the 21 pts, 6 (28.6%) were positive for p53 and there was a trend for p53 positivity to be N- and ER- and no correlation for size, grading and Ki-67 L.I. For the entire group five- and 10-year Kaplan-Meier time to progression rates were 45% and 30% and overall survival 55% and 40% respectively. No significant differences in disease-free survival (DFS) or overall survival (OS) were found with respect to size (P=0.46; P=0.35), grading (P=0.54; P=0.24), ER (P=0.64; P=0.23), PgR (P=0.54; P=0.11), and p53 (P=0.83; P=0.49) while at 5-year follow-up, node and Ki-67 L.I. were still statistically significant higher DFS (P=0.02) and OS (P=0.007) than the positive group. At 10-year only the Ki-67 L.I. was predictive of DFS (P=0.027) and OS (P=0.007). At least in this series the incidence of p53 positivity is concordant with the FBC. Our data did not demonstate groups with a useful predictor of disease-specific and overall survival. Nodal disease and Ki-67 L.I. were significant predictors of poor prognosis.

W. Chapman, D. Brown, J. Schofield, P. Jones
Mid Kent Healthcare Trust, Maidstone Hospital, Maidstone, Kent, UK

Details of the tumour size, Bloom-Richardson grade, presence or absence of vascular or lymphatic invasion of 20 successive patients with breast cancer seen over a five week period in one Breast Clinic were sent to all Fellows of the Association of Surgeons. The age of each patient was given and women over 75 were excluded. Fellows were requested to outline their surgical management and whether or not they would refer to a Clinical or Medical Oncologist.

The lymph node status in all women has been established but has not been circulated as this would assume axillary surgery which many surgeons do not perform.

Eighty-one replies were received. Disturbing variations in management were revealed with individual women being advised to undergo mastectomy by some surgeons and lumpectomy by others. Some patients would have been offered auxiliary sampling, auxiliary clearance of no axillary intervention by different surgeons, who also varied regarding their oncological referral policies.

A detailed analysis of these results will be presented for discussion.

8. Colour flow Doppler in assessment of breast disease
Z. Rayter, T. Robinson, F. C. T. Smith, M. Helliwell
Departments of Surgery and Medical Physics, Bristol Royal Infirmary, Bristol, UK

Colour flow Doppler (CFD) is a sensitive modality for detecting abnormal blood flow in malignant disease. Forty-three CFD scans were performed in 42 patients, 34 with proven (one bilateral), three with suspected breast cancer, and five with benign disease, mean age 64 (35-88) and compared with triple assessment. P-tients were scanned radially from the nipple and in transverse/axial planes using an ATL Dopper with a 7.5-3.5 mHz matrix array transducer. Scans in 20 patients were graded blind by video analysis to give a CFD index (CFDII) of 0-4 for malignancy on the basis of enhanced colour flow intensity, abnormal flow patterns and peak systolic velocities using the contralateral breast as a control. Subsequently, in 33 patients abnormal flow has been quantified by measuring the maximum peak Doppler frequencies (MPDF) in the affected and contralateral breast (34 scans—11 who initially had CFDII graded) to construct the MPDF index (MPDFII) as a measure of increased blood flow to the tumour.

Sensitivity and specificity for cancer was 100% and 25% respectively. Correlation of tumour size determined by CFD compared with histological size (r=0.97) was closer than that derived by mammography (r=0.85). The CFDII detected two tumours (histologically confirmed) in the breast of one patient with only one mammographically detected tumour. In one patient with a clinically partial response to neoadjuvant chemotherapy, a CFDII of 0 correctly predicted a complete pathological response. One patient suspected of having a local relapse because of a CFDII of 1 did not relapse confirmed by mammography and cytology, and one patient with a CFDII of 3 had benign breast disease.

The vascularity of malignant tumours was increased as evidenced by a mean MPDFII of 3.3 kHz (1-9) compared with 1.4 kHz (0.8-2.5) in the contralateral normal breast. The mean MPDFII in cancers was 2 (1-6.7) compared with 0.96 (0.6-1.25) in benign tumours. In seven of 10 patients on neoadjuvant medical therapy who have shown a response, four have also shown a decrease in MPDFII. CFDII has a role as an adjunct in the diagnosis of breast cancer and may also have a role in monitoring response to medical therapy.
9. Factors influencing the therapeutic value of fine-wire localization biopsy of breast lesions

D. R. Chadwick and A. J. Shortt
Department of Surgery, Royal Hallamshire Hospital, Sheffield, UK

Fine-wire localization biopsy is an accurate technique for determining the nature of mammographically detected breast abnormalities, and may be both diagnostic and therapeutic in the management of such lesions. Diagnostic failures are usually due to uncommon technical problems, but the factors influencing therapeutic success are poorly defined.

A number of factors were therefore examined regarding their influence upon the therapeutic success of a consecutive series of 129 localization biopsies, performed under the care of a single consultant breast surgeon. Factors included number and depth of wires inserted, hook position in relation to target lesion, breast size, type of radiological abnormality, pre-operative cytology, and grade of operating surgeon.

In situ or invasive malignancy was detected at initial localization in 65 cases (malignant/benign ratio 1.10:1; 27 (42%) achieving adequate local tumour excision margins without further surgery, and 22 (34%) demonstrating no histological evidence of residual tumour after further surgery (mastectomy in 23, further wide excision in 15). Therapeutic success was related to the accuracy of pre-operative needle localization (the needle hook being positioned within 1 cm of the target lesion in 71/72 (100%) therapeutic biopsies, compared to only 9/29 non-therapeutic biopsies in which cytology was available (P = 0.044, Chi-square)).

In patients with benign disease, biopsy weights were related only to the nature of the mammographic abnormality, being lower when excising an area of microcalcification than a mass lesion (P = 0.001; overall 64% had biopsy weight <20 g).

Localisation biopsy has a high diagnostic success rate and a therapeutic value dependent upon accurate pre-operative needle positioning, supplemented by fine-needle aspiration cytology.

10. DCIS of the breast: review of 239 consecutive cases

V. Distante, R. Simoncini, M. Rontini, F. Falli, A. Manetti, A. Valiani, C. Ponzano, L. Catalotti
Istituto Clinica Chirurgica I, Viale Morgagni 85, 50134 Firenze, Italy

Introduction: Ductal carcinoma in situ (DCIS) is more and more frequently diagnosed due to adoption of mammographic screening programs. Patients with DCIS have been treated in many different ways. Even though available data indicate that conservative surgery plus radiotherapy is a reliable method to treat DCIS, uncertainties about the most appropriate treatment of this disease are still present and different studies are ongoing.

Materials and methods: A consecutive series of 239 breast DCIS patients, from February 1968 to August 1993, were analysed to define the diagnostic feasibility and evaluate the therapeutic outcome. Clinical examination was performed in all patients. mammography in 229, fine needle cytology in 171. The therapeutic outcome was evaluated in 220 patients with a minimum follow-up of 1 year. One hundred and six women had been submitted to radical surgery, 65 to conservative surgery and 53 to conservative surgery plus radiotherapy. No difference in 5 year overall survival was found among the three groups: mastectomy 94.2% ± 2.2, conservative surgery 96.2% ± 2.6, conservative surgery plus radiotherapy 96.6% ± 2.2. Local relapse free survival was significantly different (P < 0.005) between mastectomy (98.8% ± 1.1) and conservative surgery plus radiotherapy (92.2% ± 4.4). No significant difference between conservative surgery with radiotherapy and without one appeared (92.2% ± 4.4 vs 92.3% ± 6.3).

Discussion: Our series, collected during a long period of time, confirms the tendency, already reported by other authors, toward conservative surgery. Overall survival does not seem to be affected by the type of local treatment adopted, but, on the contrary, a conservative approach, mainly if radiotherapy is not given, exposes the patients to a higher risk of local recurrence. In our experience a 10% difference in 5 year local relapse free survival occurred between the conservative surgery groups with or without radiotherapy. This was not statistically significant probably due to the low number of patients. Our data seem to indicate that neither the mammographic appearance nor the histological subtype affects the final outcome. Local recurrences after conservative surgery occurred as invasive tumours in about 50% of cases. While salvage mastectomy could be regarded as an effective treatment for DCIS recurrences, for invasive tumours it may be less effective.

11. Histological assessment of aggression in ductal carcinoma in situ

Depts of Surgery and Pathology*, Newcastle General Hospital and Glasgow Royal Infirmary, UK

The incidence of ductal carcinoma in situ (DCIS) has increased from <5% of all breast carcinomas to >25% following the introduction of screening mammography. While in the past mastectomy has produced excellent results, there is now an increasing trend towards breast conservation for invasive carcinoma and it is difficult to justify mastectomy in patients with DCIS. Unfortunately the natural history of these lesions is unknown. It appears that comedo DCIS is biologically more aggressive and more likely to recur and progress. This study examined mitotic count, nuclear grade, S-phase fraction, DNA ploidy, p53 expression and the presence of microinvasion in a consecutive series of 100 patients with DCIS to examine whether the greater tendency of comedo DCIS to recur was reflected in histological parameters. Results, see table, results given as mean (SEM) or number (%).

<table>
<thead>
<tr>
<th></th>
<th>Comedo</th>
<th>Cribriform</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>57</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Age</td>
<td>57.5 (1.2)</td>
<td>56.8 (2.0)</td>
<td>54.5 (1.9)</td>
</tr>
<tr>
<td>Mitotic count</td>
<td>12.0 (0.8)</td>
<td>3.2 (0.5)*</td>
<td>5.0 (1.0)*</td>
</tr>
<tr>
<td>Nuclear grade</td>
<td>2.9 (0.1)</td>
<td>1.3 (0.1)*</td>
<td>1.9 (0.2)*</td>
</tr>
<tr>
<td>S-phase fraction</td>
<td>9.8 (1.3)</td>
<td>7.8 (1.9)</td>
<td>6.5 (2.5)</td>
</tr>
<tr>
<td>Diploid no (%)</td>
<td>26 (46%)</td>
<td>17 (59%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>p53 positive no (%)</td>
<td>16 (28%)</td>
<td>1 (3%)*</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Microinvasion no (%)</td>
<td>13 (23%)</td>
<td>4 (14%)</td>
<td>5 (36%)</td>
</tr>
</tbody>
</table>

Statistics: Mann–Whitney U, Chi square. * P<0.05.

This study demonstrates that comedo DCIS has a significantly greater mitotic count, nuclear grade and that more patients are p53 positive than those with cribriform DCIS. In conclusion histological parameters reflect the increased biological aggression traditionally associated with comedo DCIS.

12. Sequential lymphatic dissemination of breast cancer

The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands

The purpose of the study was to examine the hypothesis that lymphatic dissemination in breast cancer occurs in a sequential fashion.

Twenty-two patients with clinically localized breast cancer were studied. Patent blue dye was administered into the tumour at the beginning of the operation. Mastectomy was carried out as usual with a complete axillary node dissection. Subsequently, the specimen was explored in the pathology laboratory. Blue stained lymphatic channels were dissected from the primary tumour to the first draining lymph nodes. These first-echelon nodes (sentinel nodes) were removed from the specimen and examined separately for the presence of metastatic disease.

In one patient with a primary tumour in the medial upper quadrant, no sentinel node was found in the axilla. Based on the direction of the lymphatic channel, drainage was presumed to have occurred to an internal mammary node. A total of 35 blue first-echelon nodes was identified in the remaining 21 patients. In 11 of these patients, the first-echelon nodes and all other axillary nodes were free of disease. In four patients, metastatic tumour was found in a first-echelon node and in or more other nodes as well. A first-echelon node was the only metastatic node in the remaining six patients. The likelihood of such a distribution of tumour-positive nodes occurring by chance is less than 0.001 (chi-square test).

This study indicates that the concept of sequential dissemination seems to be valid in breast cancer, in analogy to melanoma. Initial clinical studies suggest that the first-echelon node can also be identified in vivo. When confirmed, these data may lead to a substantial reduction of the need for axillary node dissection without compromising survival and regional control, while the same diagnostic and staging information remains available.
13. Axillary lymph node dissection for non-palpable breast cancer—248 cases

G. Le Bouedec, V. Foillié, C. Pomel, P. Keffoufman, M. de Latour, J. Dauplat
Centre Jean Perris, 58 rue Montauban, 63011 Clermont-Ferrand Cedex 1, France

A retrospective clinicopathological study concerning 248 axillary lymph node dissections for non-palpable breast cancer is reported. The mammographically screened tumors were represented by 213 invasive ductal cancers (IDC), 32 invasive lobular cancers (ILC), and three invasive mucinous cancers. Ductal and lobular cancers in situ with microinvasion have been excluded. Stellate or spiculate opacity (108 cases) was the most frequent mammographic abnormality, followed by clusters of microcalcifications (76 cases), opacity with microcalcifications (36 cases), and well-circumscribed opacity (28 cases). The histologic size of the invasive component was ≤ 5 mm in 45 cases, 6–10 mm in 106 cases, 11–15 mm in 61 cases, 16–20 mm in 19 cases, >20 mm in 16 cases. The differentiation of the IDC was classified according to Scarff-Bloom-Richardson grading system: 131 cases were grade I (61.5%), 67 cases were grade II (31.5%), 15 cases were grade III (7%). Axillary dissection was performed immediately in 196 instances (79%) or secondarily in 52 instances (21%) according to the results of intra-operative examination of surgical specimens.

Lymph nodes status was not related to the histologic type but did correlate with the histologic size. Lymph node involvement (N+) was not encountered in any invasive cancer ≤ 5 mm. Among the 248 non-palpable invasive cancers, the occurrence of N+ was 8.5% (21/248) as follows: 11.4% (11/96) in the category of tumours >10 mm, 6.5% (10/152) in the category of tumours ≤ 10 mm. N+ was found in 19 cases of the 213 IDC (8.9%), in two cases of the 32 ILC (6.2%). The percentage of axillary lymph node involvement in the subclinical IDC group was not influenced by the differentiation: 8.4% (11/131) of patients with grade I tumours had involved lymph nodes, compared with 9% (60/663) of those with grade II and 11.3% (2/15) of those with grade III. Furthermore, when the axilla contained metastatic disease, only one node was involved in 66% (14/21) of cases.

Owing its morbidity and low likelihood of N+, we questioned the value of lymph node dissection for mammographically detected invasive cancers ≤ 5 mm in maximum diameter and smaller.


M. R. Shetty
Northwest Community Hospital, Arlington heights, Illinois 60005, USA

We reviewed 1244 cases of breast cancer between 1980 and 1995 to look for incidence of axillary disease. Four hundred and forty-two cases or 35.45% had positive nodes. Two hundred and fifty-nine cases were less than 1.0 cm. The yield of axillary metastasis for tumours 0.3 cm and had positive nodes. Nineteen hundred and two hundred and sixty-five nodes were removed and 2102 of these were positive i.e. 10.9%. We also reviewed the literature for the last 60 years and found 2625 cases where tumours were less than 1.0 cm and 447 of these had positive nodes (17.0%).

The yield of axillary metastasis decreases with decreasing tumour size. The dilemma to dissect the axilla increases with decreasing tumour size.

In the US in 1995, about 35.14 times more will have tumours less than 1.0 cm. Five thousand, seven hundred and seventy-seven of these cases will have positive nodes. These cases will be missed if the axillary dissection is omitted.

15. Angiosarcoma of the breast following breast conserving therapy in The Netherlands


Purpose: National survey of the incidence of angiosarcoma (AS) after breast conserving therapy (BCT) in The Netherlands. A search for possible risk factors and prognostic factors is presented.

Methods: By means of a questionnaire sent to all Dutch radiotherapy departments, a survey of the national pathology database and of the data of the comprehensive cancer centers, we gathered detailed information concerning 21 patients with an angiosarcoma following BCT, diagnosed between 1988 and 1995.

Results: The median disease free interval between BCT and the development of AS was 75 months (29–106), median age at BCT was 60 years (36–75). In 65% of patients the primary tumour was poorly differentiated. All patients had received radiotherapy on the entire breast and a booster dose. 16 patients showed radiation induced fibrosis, six had evidence of the breast and five had telangiectatic lesions. The AS diagnosis was based on the clinical appearance by visible skin lesions; mammography and fine needle aspiration cytology were not helpful. In one patient the AS developed in the bed of the original tumour; in 77% only skin and subcutaneous tissues were involved. All AS were treated surgically. The median follow-up after treatment for AS is 47 months (9–124), the median survival for the entire group is 25 months (5–76). Ten patients experienced a relapse following a median disease free interval of 6 months. The relapse-free patients are all alive with a median disease free survival of 47 months (5–76). An initial complete resection of the AS is histologically free margin is a long disease free interval after BCT are the only significant prognostic factors. Compared to the extremely rare de novo sarcomas of the breast, the incidence of AS after BCT is far higher, suggesting a causative association with the radiation therapy. In absolute numbers the occurrence of AS is relatively low.

Conclusion: Due to the increased use of BCT over the last 15 years, the absolute number of treatment induced angiosarcomas will increase. Keys to a potentially long survival include special attention to skin lesions with a subsequent timely biopsy and complete local resection of the angiosarcoma.

16. Initial experience with transverse rectus abdominis myocutaneous flap breast reconstruction following mastectomy

J. A. Kennedy, L. McKenzie, S. J. Kirk
The Breast Unit, The Ulster Hospital Duntaldun, Dundaldun, UK

Introduction: Breast reconstruction following mastectomy diminishes the impact of mutilating surgery. In addition to lactation, the breast contributes an essential component to body form and identity. Breast reconstruction avoids this functional deficit. Reconstruction can be either by insertion of a prosthetic or use of autologous tissue transfer. Complications occurring after insertion of a prosthetic include infection, capsule formation, leakage and possibly microcambolization. The transverse rectus abdominis myocutaneous (TRAM) flap allows creation of a neo-breast without the need for an implant. We describe our initial experience of TRAM reconstruction.

Methods: Nineteen patients (median age 46 years (range 27–75)) underwent TRAM reconstruction. In 84% (16/19) this was performed immediately at the time of mastectomy. Two patients required simultaneous contralateral reduction mammoplasty to achieve satisfactory symmetry. Indications for surgery were invasive breast cancer in 85.9% (17/19) and extensive ductal carcinoma in situ in 2/19.

Results: Surgery was completed in all patients, median operation time 5.1 hours (range 4.5–8.5). Median post-operative stay was 9 days (range 6–26). There were no major complications. A degree of skin loss occurred in seven patients. This was < 10% in 57. Four patients required minor wound revision under local anaesthesia. Post-operative adjuvant treatment was given on the basis of original staging criteria. At follow up (median 16.5 months (range 4–29)) all patients had a satisfactory cosmetic result with no evidence of local recurrence.

Conclusions: In our unit immediate breast reconstruction employing the TRAM technique forms an integral part of the management of breast cancer. Our preliminary data suggests that reconstruction does not compromise the initial procedure, subsequent treatment or outcome particularly when performed by one surgical team.

17. Bone metastases express increased levels of PTHrP and its receptor in breast cancer patients

S. E. Downey, J. Hoyland, A. J. Freemont, N. J. Bundred
Department of Surgery, University Hospital of South Manchester, UK

Parathyroid hormone related protein (PTHrP), an osteolytic factor secreted by osteoblasts and tumour cells, is reported to predispose to bone metastasis. To determine whether expression of PTHrP or its receptor specifically enhance tumour cell survival in bone, we studied their expression in primary breast cancers and breast cancer metastases in bone and lung. In situ hybridization was used to identify the mRNA for both PTHrP and its receptor. The cDNA probes were labelled with 35S and control slides treated with crude RNAse. Tumours were scored by two investigators using intensity of signal (1–3) and number of positive tumour cells (1<20%, 20%<2<80%, >80%).

Levels of PTHrP and its receptor mRNA were significantly higher in bone metastases than in primary breast cancers and normal bone. Levels of PTHrP and its receptor mRNA were significantly higher in bone metastases than in primary breast cancers and normal bone.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Receptor mRNA score</th>
<th>Protein mRNA score</th>
<th>Both mRNA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>100% (33/33)</td>
<td>63% (28/43)</td>
<td>26% (9/35)</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>53% (8/15)</td>
<td>25% (5/15)</td>
<td>2% (1/50)</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>53% (8/15)</td>
<td>25% (5/15)</td>
<td>2% (1/50)</td>
</tr>
</tbody>
</table>
metastases than in primary breast carcinomas (protein: P = 0.0379; receptor: P = 0.0008) but significantly lower in lung metastases (protein: P = 0.0027; receptor: P = 0.0003). Osteoblasts in bone metastases overexpressed PTHrP mRNA compared to normal bone. Overexpression of both PTHrP and its receptor in breast cancer cells produces site specific metastases in bone due to autocrine/paracrine growth stimulation by PTHrP.

PTHRP = parathyroid hormone related protein, CDNA = complementary deoxyribonucleic acid, mRNA = messenger ribonucleic acid.

18. Neo-adjuvant chemotherapy (FECC50/FAC50 drug regimen) for conservative surgery in large-sized operable breast carcinomas: a 38 cases series

Paul Strauss Cancer Center, 3 Rue de la Porte de l'Hôpital, 67085 Strasbourg, France

Background: Despite the development of breast-sparing procedures, modified radical mastectomy (Patey procedure) remains the conventional treatment of large-sized, non-inflammatory and non-metastatic, invasive carcinomas.

Patients and methods: In order to substitute conservative surgery for mastectomy and preserve body integrity, a neo-adjuvant chemotherapy was administered between September 1987 and April 1995 in 75 females with operable infiltrating breast cancer larger than 3 cm with AVCP, ACMF, CMF and, recently, with FECC50/FAC50 drug regimen in 38 cases. The median age of the 37 evaluable patients of this last homogeneous group was 49.5 years (range 28-66). Average clinical tumour diameter was 4.55 cm (range 3-8 cm). Histopathologic determination, assessed by trucut needle biopsy, revealed 30 (81%) infiltrating ductal carcinomas and seven lobular invasive carcinomas. Grading distribution was as follows: four grades II, 13 grades III, 14 grades IV, six unknown grades. Hormone receptor determination was positive for estrogen and progesterone in, respectively, 17 and 16 cases. Tumour distribution (TNM, UICC 1987) was as follows: 26 T2 (>3 cm) and 11 T3 with an axillary node status N0 in 16 cases and N1 in 21 cases. A prior axillary node dissection (average number of nodes sampled: 13-range 8-30) was performed in 23 cases (62.2%) with an histologic involvement rate of 56.5% (13/23). Axillary spread exceeded three nodes in six cases (46.1%).

Results: An objective response (complete [19%] or partial [48.6%]) to neo-adjuvant chemotherapy was noted in 25 cases (67.6%). A breast conservative treatment was performed in 69.2% (n = 18) and 54.5% (n = 6) of patients with T2 and T3 tumours, respectively. Thirteen patients (35.1%) with a residual tumour exceeding 3 cm after induction chemotherapy were treated by radical surgery. Histopathologic complete response was achieved in three cases (8.1%). External beam radiotherapy, adjuvant chemotherapy and hormone therapy were given in 37 (100%), 16 (43.2%) and 21 (56.7%) cases, respectively.

Conclusion: Although encouraging, the results of this multidisciplinary therapeutic approach remain preliminary. Nevertheless, a longer follow-up is required to evaluate the impact of this strategy on the effective long-term breast conservative rate and the survival, especially in patients responsive to induction chemotherapy.

19. Aromatase inhibition and oestrogen suppression with Arimidex™ (anastrozole), a new treatment for advanced breast cancer in postmenopausal women: comparison with other aromatase inhibitors

M. Dowsett*, P. E. Lomning, J. Geider, N. King, L. Ottestad, S. Landgren, P. L. Walton, P. O. Kormeset
*Department of Academic Biochemistry, Royal Marsden Hospital, UK

Since the introduction of aminoglutethimide (AG) in the early 1980s, oestrogen suppression using aromatase inhibitors (AIs) has become an established approach for the treatment of advanced breast cancer (ABC) in postmenopausal women. Whereas the use of AG has been limited due to its lack of selectivity and associated toxicity, newer aromatase inhibitors such as the third generation AI, 'Arimidex' (anastrozole), offer good tolerability alongside greater potency and improved convenience. Whole body aromatase inhibition and plasma oestrone suppression were determined for anastrozole 1 and 10 mg o.d in a double-blind crossover trial in postmenopausal women with ABC. Aromatase activity was suppressed by 96.7% and 98.1% with anastrozole 1 and 10 mg respectively, and plasma levels of oestrone, oestradiol and oestrone sulphate were suppressed respectively by ≥85.5%, ≥83.3% and ≥93.5% irrespective of dose. Thus anastrozole was highly effective in inhibiting in vivo aromatization with no statistically significant difference in efficacy between the two doses, and additionally showed consistency between the percentage aromatase inhibition and suppression of plasma oestrogens. We have also reported aromatase inhibition and oestrogen suppression data for AG (first generation AI), the second generation AI formestane (4-hydroxyandrostenedione) and for the third generation AIs fadrozole and letrozole. AG and formestane at the conventional clinical doses appear to be less effective than anastrozole, inhibiting aromatase activity by 90.5% and 84.8% respectively, and reducing oestradiol by 75.7% and 46.4% respectively. Like anastrozole, the other third generation AIs are highly potent with respect to aromatase inhibition and oestrogen suppression; at a dose of 2 mg b.d fadrozole suppressed aromatase by 91% and reduced serum oestradiol by 72%; whilst letrozole at a dose of 0.5 mg and 2.5 mg o.d inhibited aromatization by 98.4% and >98.9% and reduced plasma oestrogens by >80%.1 From these data it is clear that anastrozole is a highly potent AI, showing activity that is comparable to other third generation AIs. It remains to be established whether this increased activity leads to increased clinical benefit compared with the earlier AIs AG and formestane.

References

128. Do reductions in superoxide dismutase (SOD) activity precede morphological change in human breast cancer?

Endocrine Laboratory, Dept of Medicine & Therapeutics and Surgery (St Vincent's Hospital), University College Dublin, Ireland

The enzyme SOD forms the cells’ principal defence against the potentially damaging effects of oxygen free radicals (O·). Alterations in the activity of this enzyme which catalyses the removal of O· has been reported in a variety of malignancies including breast cancer. The aim of this study was to compare SOD activity in the tumour centre with that in morphologically normal tissue remote from the tumour but within the tumour bearing breast. In humans SOD exists in two forms: as copper zinc (CuZn-SOD) and manganese (Mn-SOD). A total of 24 patients, eight with benign breast disease (fibroadenomas) and 16 with breast cancer were included. SOD activity (U/ml protein) in breast tissue homogenates was measured by its ability to inhibit O· generated by the xanthine-xanthine oxidase free radical generating system.

<table>
<thead>
<tr>
<th></th>
<th>N Total SOD</th>
<th>CuZn-SOD</th>
<th>Mn-SOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour Centre</td>
<td>16</td>
<td>65.5 ± 10.6</td>
<td>51.2 ± 8.3</td>
</tr>
<tr>
<td>Tumour Remote</td>
<td>16</td>
<td>117.6 ± 13.6</td>
<td>95.3 ± 12.0</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>8</td>
<td>76.6 ± 11.8</td>
<td>65.6 ± 11.8</td>
</tr>
</tbody>
</table>

The above table illustrates the total SOD activity in the tumour centre (65.5 ± 10.6 U) was significantly lower than that in remote sites (117.6 ± 13.6 U; P<0.005), due to reduced CuZn-SOD and Mn-SOD activity in the tumour centre. SOD activities in areas remote from the tumour were greater than in benign fibroadenomas, although the difference did not reach statistical significance. The results demonstrate SOD activity to be lower in breast cancer and suggest that alterations in SOD activity may have a role in tumour aggressiveness in human breast cancer.
20. Flow cytometric assessment of rectal tumours assists in the definition of poor and good prognostic groups

U. A. Khimaira, K. W. Robertson, T. G. Cooke, I. G. Finlay and D. Hemingway
University Dept of Surgery, Royal Infirmary, 10 Alexandra Parade, Glasgow, G31 2ER, UK

Curative local resection of rectal carcinoma requires that there be no lymph node metastases (LMN). Identification of a high risk of LMN may influence patient management. We have assessed a number of tumour features for association with the presence of LMN. Fifty rectal carcinomas treated by conventional curative resection were studied with flow-cytometric measurement of ploidy and DNA index. Routine pathology reports provided a measure of tumour size and differentiation. Sixteen (32%) of the patients had LMN. Depth of tumour invasion was determined histologically as within the bowel wall and extending through bowel wall. Tumour size was not associated with LMN (Mann-Whitney U test, P = 0.795). Ploidy was not associated with LMN (x^2 = 2.295, df = 1, P = 0.138), however DNA index of greater than 1.5 was significantly associated with LMN (x^2 = 6.359, df = 1, P = 0.012). Invasion outwith the bowel wall was associated with LMN (x^2 = 6.494, df = 1, P = 0.011). There was a trend toward an association between poorer differentiation and LMN (x^2 = 5.895, df = 2, P = 0.0525). Only 13 (26%) of the tumours were considered other than moderately differentiated; the value of this indicator, in this study, for identifying clinically useful prognostic groups is therefore poor. The table shows the value of measurement of ploidy and depth of invasion.

<table>
<thead>
<tr>
<th></th>
<th>Diploid or Aneuploid</th>
<th>Diploid</th>
<th>Aneuploid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within bowel wall</td>
<td>2/19</td>
<td>0/7</td>
<td>2/12</td>
</tr>
<tr>
<td>Through bowel wall</td>
<td>14/31</td>
<td>4/13</td>
<td>10/18</td>
</tr>
<tr>
<td></td>
<td>x^2 = 9.190</td>
<td></td>
<td>P = 0.027</td>
</tr>
</tbody>
</table>

The table entries are numbers of tumours with LMN over total tumours in the defined group.

Our results suggest that flow cytometric analysis of rectal tumours can help to identify patients at higher risk of LMN (DNA Index >1.5). Additionally, we show that ploidy may add to the value of depth of invasion in separating prognostic groups. Depth of tumour invasion can be assessed pre-operatively using trans-renal ultrasonography and flow cytometry can be performed on routine biopsy specimens, thus the probability of LMN can be determined prior to the primary surgical procedure.

21. Is 111-In a suitable isotope for intra-operative radioimmunolocalization of primary and metastatic colorectal neoplasms? A preliminary experience

S. Sandrucci, A. Moligia, B. Musa, M. Baccaglai, P. G. de Filippis, A. Musa

Since its proposal in 1986, intra-operative radioimmunolocalization of colorectal neoplasms with murine MAbs marked with 125-I or 111-In has been widely accepted for clinical use in detecting occult node and distant metastases. 125-I has the disadvantage of not allowing external imaging, has been widely accepted for clinical use in detecting occult node and distant metastases. 125-I has the disadvantage of not allowing external imaging, and has been included in this study. The use of 111-In labelled MAbs allowed us to achieve a 96% sensitivity and a 91% specificity. Sixteen percent of microscopic lesions not clinically apparent were easily overcome these problems; however, if used as a label on a whole antibody, the activity in the target tumour decays at about the same rate as hepatic lesions or gastroepiploic ligament nodes, as the background is unacceptably high.

22. Endothelin-1 production and secretion by colorectal cancer

Department of Surgery, UCL Medical School, London. *The Analytical Unit, St George's Hospital Medical School, London, †Department of Anatomy, UCL Medical School, London

Endothelin-1 (ET-1), a vasconstrictor peptide, has been implicated as a tumour growth stimulator. To assess its importance in colorectal cancer, immunoelectron microscopy (EM) for ET-1 was performed on colorectal liver metastases and normal hepatic tissue (n = 8). In addition plasma levels of both ET-1 and Thrombomodulin—a marker of endothelial damage—were measured in patients with colorectal cancer, with and without liver metastases and compared with an age and sex matched control group. ET-1 of the normal liver showed poor staining for ET-1 endothelial cells, whilst endothelium, tumour cell nests and extending beyond myofibroblasts within the tumour stained densely. Plasma levels of ET-1 in the control group (n = 22) gave a mean of 2.6 pg/ml (SD = 1.23). Plasma levels of ET-1 were elevated in patients with colorectal liver metastases (n = 15, mean = 4.6 pg/ml, SD = 1.75) and in those without metastases (n = 11, mean = 3.8 pg/ml, SD = 1.14), P < 0.001 and P = 0.02 respectively. Thrombomodulin levels were similar in all groups, indicating that changes in ET-1 levels were not due to damaged endothelium.

These results indicate that primary colorectal cancer and colorectal liver metastases produce ET-1. ET-1 may modulate tumour vascular tone or act as a direct growth stimulator.

23. Initial clinical experience with the biofragmentable anastomosis ring Valtrac for intraperitoneal bowel surgery

T. Kovacs, I. Kovacs, Z. Sulyok, I. Beszynyi
Department of Surgery, National Institute of Oncology, Budapest

In the present initial experience and early results in clinical application of the VALTRAC biofragmentable ring (BAR). From 11/1993 to 03/1996 we used the BAR device in 38 cases performing one gastrojejunal, four jejunoileal, five small bowel-colon and 26 intraperitoneal colonic anastomoses. All patients were operated on for malignant diseases and they received conventional (mechanical, dietary and antibiotic) bowel preparation. Intra-operative technical difficulties occurred in six patients (purse string failure, serosal split); in two cases the BAR placement was abandoned. Post-operative complications related to the BAR occurred in three patients: clinically relevant anastomotic leakage appeared in two cases (5.55%), and one case of mechanical ileus occurred. This was produced by distorsion of the inserted ring. We had no other post-operative complications. Mean post-operative hospital stay was 8 days. According to our initial experience and literature data, using the new anastomosis ring can give a good alternative to hand-sutured or stapled anastomoses.


M. M. Sousa, L. Santos, E. Ferreira, C. Lopes and G. dos Santos
Instituto Portugu?o de Oncologia Francisco Gentil, Centro do Porto, Rua Dr Ant?nio Bernardino de Almeida, 4200 Porto, Portugal

The aim of this study is to identify the clinical and pathologic prognostic factors related to local and distant recurrence of rectal cancer. We reviewed 177 cases admitted in Portuguese Institute of Oncology-Porto from January 1980 to December 1989 and treated with curative intention. Overall survival, disease free survival and recurrence location were analysed in relation to the following prognostic factors: age, sex, tumour location,
25. The type of K-Ras mutation determines prognosis in colorectal cancer: preliminary results of a prospective study

Department of Surgery and Pathology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Initiation and progression of colorectal adenocarcinomas are related to mutations involving various oncogenes and tumour suppressor genes. Mutations involving the proto-oncogene K-Ras have been described in colorectal cancer and may be related to tumour aggressiveness. The value of K-Ras gene determination as a prognostic marker is however not yet clearly established.

We conclude that an elevated bile CEA level at the time of surgery may be a poor marker. This hypothesis was evaluated in three groups of CRC patients:

Group 1 (n=55): patients who underwent a curative resection of a primary tumour.

Group 2 (n=12): patients with a suspected liver lesion but normal serum CEA level.

Group 3 (n=24): patients considered free of disease (normal ultrasonography of the liver and normal serum CEA) who underwent laparotomy e.g. for closure of a colostomy.

In Group 1 an elevated CEA level was found in 39 patients (71%). After a median follow-up of 30 months only seven patients have developed liver metastases. We assume that the biliary CEA in these 39 patients is, at least partly, also derived from the primary tumour.

In Group 2 the lesion was found to be benign in six patients. All had a normal biliary CEA level. The remaining six patients with metastases had an elevated biliary CEA level.

In Group 3 an elevated CEA level was found in seven patients. At laparotomy recurrent tumour was found in three of them. Three more patients had tumour recurrence within the next six months. Of the remaining 17 patients with a normal biliary CEA level only one has developed a recurrence (median time of follow-up one year).

In conclusion: Biliary CEA levels are of no use if bile samples are taken during primary tumour resection. If taken during follow-up these levels can be used in the diagnosis of suspected liver lesions or to predict tumour recurrence at an early stage.

26. Bile carcinoembryonic antigen and outcome following curative surgery for primary colorectal cancer

Department of Surgery and Biochemistry, Western Infirmary, Glasgow, UK

Colorectal cancer is one of the most common cancers in the Western world. Approximately 30% of patients will develop hepatic metastases following curative surgery. Pathology remains the only method of determining outcome following curative surgery. Carcinoembryonic antigen (CEA) is a well-recognized marker for cancers of the gastrointestinal tract and can be measured in serum and bile. We present 30 patients who had bile CEA levels measured at primary surgery, and who have been followed up for a median of 51 months (range 1–67 months).

Bile was obtained at surgery by trans-hepatic gallbladder aspiration and CEA levels measured by immunoassay. All patients had primary resections. Thirteen patients remain alive with no evidence of disease, and two have died of other causes. Fifteen patients are either alive with or dead of disease.

The median bile CEA level in the disease-free group is 15 μg/l (interquartile range 5.0–70) as compared to (04 μg/l (IQR:5-545) in the group with disease.

As a conclusion, elevated bile CEA level at the time of surgery may be a poor prognostic indicator following surgery for colorectal cancer. Further work is required to fully define this as a prognostic indicator.

27. The prognostic value of biliary CEA levels in colorectal cancer

M. A. Paul*, J. J. Visser, C. Mulder, G. J. van Kamp†, S. Meijer
Dept of Surgery and 'Clinical Chemistry, Free University Hospital, Amsterdam, The Netherlands

Accurate and early detection of liver metastases remains a significant clinical problem. Recently it was suggested that high biliary levels of Carcinoma-embryonic Antigen (CEA) as found in patients with liver metastases might

M. Dahllöf, L. Pihlman, B. Bergström, B. Gillenius
Dept Surgery, Oncology, and Statistics, University Hospital, Uppsala, Sweden

Background: The introduction of a more radical surgery for rectal cancer, total mesorectal excision (TME), has been claimed to improve treatment results. However, no randomized trials have been done, and thus firm scientific evidence is lacking. Adjacent radiotherapy has also been introduced with the same purpose, and several recently published randomized trials have been found to influence survival.

Method: Between 1985 and 1989, the University Hospital, Uppsala was the only hospital in Sweden combining pre-operative radiotherapy with TME. To explore whether or not this changed primary treatment had an impact on outcome, the survival of 94,262 patients with colorectal cancer in the total Swedish population between 1960 and 1989 was analysed with respect to different five years in periods.

Results: A continuous improvement in the whole country regarding relative survival was seen during the first year of follow-up for both colon and rectal cancer. However, no improvement was seen between years 1 to 5 except for the last period (1985–89), where a significant improvement in rectal cancer death rate was seen in the county of Uppsala, but not in the rest of Sweden. Similar effect on survival was seen for colon cancer.

Conclusion: This study indicates that a change in treatment strategy (TME-surgery and radiotherapy) results in improved long-term survival. However, it is not possible to estimate the size of the improvement caused by pre-operative radiotherapy and TME-surgery.

31. Effect of combined pre-operative radio-chemo-therapy on resectability of locally advanced rectal cancer

B. Rau, P. Wust, A. Friedemann, J. Löffel, J. Gellermann, R. Felix, H. Riese, P. M. Schleg
Robert Rössle Hospital at the Max-Delbrück-Center for Molecular Medicine, Humboldt University of Berlin, 13122 Berlin, Germany

Purpose: Recent studies suggest that pre-operative radio-chemotherapy in locally advanced rectal cancer can increase resectability and may improve local control in unresectable cases. Additional treatment with regional hyperthermia appears suitable for intensifying pre-operative radio-chemotherapy in those patients. We investigated the feasibility and effectiveness of regional hyperthermia with radio-chemotherapy (HRCT) for the treatment of locally advanced rectal cancer.

Patients and methods: Thirty patients with histologically proven primary rectal cancer entered the trial. Initial tumour stage was assessed by endosonography (ES) and computed tomography (CT) as cT1-3cN1. Pre-operative radiotherapy (33 Gy in 5 fractions) was performed in the prone position under general anaesthesia and followed by chemotherapy with fluorouracil and leucovorin. Pre-operative 5-fluorouracil (300-500 mg/m²) and low dose leucovorin (50 mg) were administered on days 1-5 and days 22-26. Regional hyperthermia (RHT) was carried out using the annular phased array applicator SIGMA 60, BSD-2000) once a week prior to radiotherapy. Radiotherapy was delivered 15-20 minutes after RHT and was performed in the prone position using belly board, three-field technique, individualized standard blocks, in a fractionation of 5 x 1. 8 Gy up to 45 Gy in five weeks. Re-staging was done by ES and CT. Four weeks after radiotherapy, surgery was performed. If the tumour remained non-resectable or any other risk was encountered, usually the total tumour dose was boosted to 60 Gy.

Results: Grade III toxicities occurred at the intestine in 33% and at the skin in 5/30 patients, respectively. In three patients substantial of the pre-operative treatment course was required for less than five days. One patient refused further RHT because of claustrophobia. No serious complication could be attributed to hyperthermia. The overall resectability rate was 25/30 patients (83%); of these 23/30 proved R0-resectable. 19/30 (63%) had downstaging (CR n=4 patients/PR n=15 patients) from the initial endosonographic tumour stage during pre-operative therapy. The response correlated with the quality after 30 months is 80%. Among the five patients with non-resectable carcinomas, two patients achieved long-term stable disease with a range of 14-27 months.

Conclusion: Pre-operative RHT is feasible and effective, causing an encouraging response rate of 80% and resectability rate of 83% of locally advanced rectal cancer. Toxicity is moderate, and no severe complications were found during the pre- or peri-operative course. Our results suggest that hyperthermia in addition to radio-chemotherapy can improve local tumour control.

32. RIGS (radioimmunoguided surgery) for colorectal cancer surgery

S. Schneebaum, J. Pappo, M. Graif, M. Baratz, J. Baron, Y. Skornick
Ichilov Hospital, Tel-Aviv Sourasky Medical Center, Sackler School of Medicine, Tel-Aviv University, Israel

There is an emerging reluctance for doing radical surgery for colorectal cancer due to failure so far to demonstrate improved survival with randomized surgery. Radioimmunoguided surgery (RIGS) is an intra-operative diagnostic method based on monoclonal antibodies (MoAb) labeled with a radioactive isotope (I131). Forty patients with colorectal cancer (26 recurrent, 14 primary) were injected with a 2nd generation anti-TAG (anti-tumour-associated glycoprotein) MoAb, CC49 121, three weeks prior to surgery. Pre-operative workup included colonoscopy (with surgery), CT of the surgeon's traditional exploration and confirmed by pathology. In 11/40 patients (27.5%) RIGS detected occult findings (not identified by either CT of the surgeon's traditional exploration and confirmed by pathology). In 10/22 recurrent patients (38.4%), and 11/14 primary patients (7.0%), occult findings included: metastasis in lymph nodes, anastomotic recurrence, pelvic tumour, uterine and peritoneal metastases. This resulted in changing the surgical plan in 12/40 (30%) patients—either by extending surgical resection, or by eliminating unnecessary surgical procedures. These results suggest that RIGS offers a substantial benefit for patients undergoing surgery for colorectal cancer, leading to a more rational approach in guiding the surgeon when selecting radical or non-radical surgery in a non-randomized way.
with colorectal cancer. This work is supported by an educational grant from Zeneca Pharmaceuticals.

34. Abdominoperineal rectal excision versus sphincter-saving rectum resection for lower third rectum cancer

F. Penning, T. Topal, L. Flize, R. Aerts, R. Kerremans
Department of Abdominal Surgery, University Clinic Gasthuisberg, Herestraat 49, 3000-Leuven

Background: The type of curative surgery for rectal cancer in the lower third is controversial. Generally, abdominoperineal rectum excision (APRE) is advocated, although sphincter-saving operations (SSO) may be equivalent provided a 2 cm distal safety margin (i.e. 4 cm in vivo) is obtained. Taking into account a 2 cm length of the anal canal, this means that only tumours at ≥2 cm above the anal verge would permit an SSO. In practice, however, this theoretical rule is not always respected. Therefore, we compared the late outcome after APRE and SSO for rectal adenocarcinoma located at ≥6 cm versus at <6 cm above the anal verge.

Patients: Ninety-nine consecutive patients (M/F 64/35; 63 yrs) with rectal adenocarcinoma at <8 cm who underwent primary ‘curative’ surgery (R0/M0) between Jan. 1984 and Dec. 1993 were studied. Exclusion criteria were: pre-operative chemoradiation for downstaging (6), intra-operative tumour spillage (12), post-operative chemoradiation (7). Follow-up was complete. Patients dying in the post-operative period (1/99; after APRE) were taken into account when studying the cancer-related survival rate, but not to determine the local recurrence rate.

<table>
<thead>
<tr>
<th>APRE</th>
<th>SSO &lt;6 cm</th>
<th>SSO ≥6 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of Pts</td>
<td>57</td>
<td>42</td>
</tr>
<tr>
<td>Stage 1/2/3</td>
<td>15/24/18</td>
<td>1/14/13</td>
</tr>
<tr>
<td>Differentiation (W/M/P)</td>
<td>15/32/10</td>
<td>7/7/7</td>
</tr>
<tr>
<td>Local recurr. rate</td>
<td>27%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Results: The survival rate after APRE and SSO was 95% vs 98% at 1 yr, 85% vs 90% at 2 yr, 61% vs 67% at 5 yr.

Conclusion: recurrence and cancer-related survival rates after APRE and SSO for rectal cancer below 8 cm were comparable. SSO for cancer at ≥6 cm had the same outcome as SSO for tumours at <6 cm. Post-operative leak did not affect the outcome. These results were obtained in a consecutive patient series operated and in 71% (129 cases) of these an R0 resection was performed.

35. Survival and recurrence after R0 resection for distal rectal tumours

J. C. Mendes de Almeida, P. Chaves, P. Fidalgo, P. Lage, L. Manoel, A. Barata, J. M. Mendes de Almeida
Instituto Portugues de Oncología—Centro de Lisboa, Departamento de Cirurgia, Dr. J. M. Mendes de Almeida, Rua Prof. Lima Basto, 1093 Lisboa, Portugal

Survival and recurrence rate in lower 1/3 rectal tumours are determined by several patient and tumour factors, and possibly also by treatment options. In order to evaluate currently available prognostic factors for these tumours, patients submitted to R0 resection (UIJC) in our department were retrospectively analysed.

From Jan. 1989 to Dec. 1993, 192 patients with rectal carcinoma were operated and in 71% (129 cases) of these an R0 resection was performed. In 38 cases (46%) the tumour was located in the distal 1/3 of the rectum, this last group being the object of the present study. Gender distribution was of 34 men (59%) and 24 women (41%), with a median of 64 years (min.: 36; max.: 82). TNM staging (UICC) was: St. I—44%; St. II—26%; St. III—38%; St. IV—2%. The operations performed were: anterior resection with colo-anal anastomosis—6 cases (10%); Abdomino-perineal resection—49 cases (84%); Posterior exenteration—1 case (2%); Hartmann procedure—2 cases (4%). Morbidity was noted in 39 patients (67%) and three of these cases eventually died (5%). In 18% of these patients, adjuvant therapy was used. All patients were available for follow-up. To determine prognostic impact on survival and recurrence, 19 variables were evaluated:

<table>
<thead>
<tr>
<th>N of Patients</th>
<th>223</th>
<th>216</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response (CR + PR)*</td>
<td>19.3%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Median TTP (m) [95% CI]</td>
<td>4.8 [3.1–5.3]</td>
<td>3.6 [3.0–5.3]</td>
</tr>
<tr>
<td>Median survival (m) [95% CI]</td>
<td>10.3 [8.3–11.7]</td>
<td>10.3 [9.1–11.7]</td>
</tr>
</tbody>
</table>

* Odds ratio = 1.2 (95% CI 0.73–1.97), P = 0.48.

There was no statistically significant difference between the two treatment arms in any of the efficacy endpoints. However, a statistically significantly higher incidence was seen of WHO Grade 3 and 4 leucopenia (30% vs 14%) and mucositis (22% vs 2%) in the 5FU + LV patients and of reversible transaminase increases (10% vs 0%) and anaemia (9% vs 2%), in the Tomudex patients. The transaminase rises were largely asymptomatic and resolved under ongoing therapy. More than 70% of the patients in the study showed palliative benefits. These benefits were at least as frequent in the Tomudex group as in the 5FU + LV group (no change/improvement in performance status 84% vs 75%, no change/gain in weight 86% vs 72%). We have concluded that the final analysis of this international study confirms that Tomudex has similar efficacy and an acceptable safety profile when compared to a standard regimen of 5FU + LV in the palliation of ACC, and has the advantage of offering more practical and convenient administration.

'Tomudex' is a trademark, the property of Zeneca Limited.
37. Oxaliplatin (L-OHP) ± 5-fluorouracil (5-FU) in refractory, metastatic colorectal cancer patients

E. Mauzone, F. de Braud, E. Coccocchini, F. Nolè, D. Michelich and M. S. Aspro
European Institute of Oncology, Via Ripamonti 435, 20141 Milano, Italy

L-OHP is a new non-cytotoxic platinum derivative, active and very well tolerated in pretreated advanced colorectal cancer patients (pts). The addition of 5-FU + leucovorin (LV) to L-OHP increases the response rate from 10% to 40% (28%±53%). To further demonstrate the importance of L-OHP, we performed a phase II study in which L-OHP, at the dose of 130 mg/m², over 2 hours i.v. q 3 weeks, was started as a second-line treatment after 5-FU failure, or added to the ongoing 5-FU containing regimen. To date 22 pts have been enrolled: 21 are evaluable for toxicity and 19 for response (2 too early; one lost to follow-up); all pts had showed progressive disease during 5-FU treatment, four in an adjuvant setting and 18 for metastatic disease. Patient characteristics: median age = 60 years, (45-76), malnefemale 12/10, PS 0/1/2 in 5/16/1 pts. All pts had measurable metastatic disease: liver was involved in 17 pts, lung in 10 pts, lymph-nodes in three pts. Other sites included pelvis, peritoneum, pleura and bone. No grade 4 toxicity (according to the NCI-CTC) has been observed and only three pts developed a grade 3 diarrhea. Nausea and vomiting occurred in 41% of the cycles as a grade 1, and in 27% as a grade 2. Grade 2 haematological toxicity has been reported in 15% and 3% of the cycles for neutrophils and platelets respectively. The most common toxicity was neurologic (grade 1 and 2 in 57% and 10% of the cycles respectively) as hand-foot paresthesias or hyporeflexia to cold. Pts were treated for a median of three cycles (1-9) and for a median period of 3 months (1-8). Dose reduction was performed in two pts (two cycles). Among the 19 pts evaluable for response (WHO criteria) we observed 4 PR when L-OHP was added to the previously unsuccessful 5-FU containing regimen, for an overall RR of 21% (95% CI: 3%-39%).

38. Jejunal pouch reconstruction after total gastrectomy. A long-term evaluation

B. Miclai, M. A. Goffio, F. P. Saitta, M. Bartolotta, R. R. Pidota, G. Versaci
General Surgery, University Policlinic “G. Mariano”, Pavia, Italy

The best type of digestive reconstruction following total gastrectomy (TG) for gastric malignancy (GM) is still controversial. The Roux-en-Y (RY) remains the most widely used method, however malnutrition, adverse symptoms and derangement in quality of life are frequently observed. The modification of the standard RY by jejunal Hunt-Lawrence-Rodino pouch or J-pouch (JP) seems to reduce the effects of gastric loss. In order to improve the advantages of the JP method we adopted a modification consisting in the construction of a second pouch in the distal part of the Roux limb.

Patients and methods: Twenty-three patients with GM who had undergone between 1990 and 1995, D1-D2 TG and double-pouch (DP) reconstruction were assessed in order to determine the advantages of (a) reservoir function; (b) RY symptoms; (c) quality of life. Seven patients similar for age, primary disease and surgical treatment except for a simple RY reconstruction were compared. The patients were evaluated for at least 6 months after operation with a mean follow-up of 37.8±13.7 months. Follow-up studies consisted in endoscopic examination, blood count, serum proteins (SP), actual body weight (BW) and symptoms (Cushieri's scoring (CS)).

Results: No operative deaths were observed. There were 18 survivors without evidence of recurrence. Oesophageal mucosal changes (hyperemia, erosion, ulcers) documented similarly in both groups (39% vs 43%). A gain in BW was recorded in 83% of DP group compared with 71% of RY groups (NS). Analysis of CS revealed a score of 4.4±1 in DP group with a significant difference compared to RY groups (13.6±2.23.3±0.01) of RY group.

Because of the higher quality of life observed in DP group, the reconstruction by a double-pouch procedure can be recommended.

39. Adenocarcinoma of the gastro-oesophageal junction—results of surgical therapy between 1974 and 1993

T. Horbach, W. Hohenberger, J. Göhl, P. Klein, K. Göthner, A. Altenhoff-Hoffmann
Department of Surgery, University Hospitals, Maximalinsplatz, D-91054 Erlangen, Germany

We performed an analysis of all patients with an adenocarcinoma of the gastro-oesophageal junction who were treated in our clinic during the time intervals 1974 to 1983 and 1984 to 1993.

Carcinoma of the cardia made up about 20% of all carcinomas of the stomach (260/1303 respectively 190/1007) in both time periods. Curative resection (R0) was carried out in 53.1±7.9%. Post-operative mortality decreased from 16% (1974-83) to 6% (1984-93). Carcinoma of stage UICC (NS). Analysis of CS revealed a score of 4.4±1 in DP group with a significant difference compared to RY groups (13.6±2.23.3±0.01) of RY group.

Because of the higher quality of life observed in DP group, the reconstruction by a double-pouch procedure can be recommended.

40. Neoadjuvant chemotherapy for advanced oesophageal carcinoma: a retrospective study of 38 cases

Clínica Oncológica 4º Piso, Instituto Português de Oncologia-Porlo, R/Dr Antonio Bernardino de Almeida, 4200 Porto, Portugal

Thirty-eight patients with locally advanced squamous cell carcinoma of the oesophagus who had undergone a preoperative CTG between January 1987 and October 1992 were included. Risk factors, nutritional status, performance status (PS), extent of disease, preoperative staging and high standard of operative technique and lymph node dissection. Therefore since 1995 we use an optimized scheme for the dissection based on the Japanese recommendations which will be demonstrated during the presentation.

41. Neoadjuvant chemotherapy for advanced oesophageal carcinoma: a retrospective study of 38 cases

E. Munzone, F. de Braud, E. Coccoroccio, F. Nolè, D. Micheli and M. S. Aspro
GazzAr 1-98125 Messina, Italy

The share of Barrett’s carcinoma in all surgically treated oesophageal cancer patients (pts) is still controversial. The Roux-en-Y (RY) reconstruction by a double-pouch procedure can be recommended.
41. Long-term results of resected oesophageal cancer with complete remission to pre-operative chemoradiation

J. P. Triboulet, H. Amendt, Ch. Rey, M. Lecomte-Houcke
Service de Chirurgie Générale et Endoscopie (Pr. C. Praye), Hôpital Cl. Huriez, 9037 Lille Cedex

Introduction: Improvement in the results of combined chemoradiotherapy (CCR) in oesophageal cancer has led several groups to adopt a non-surgical approach particularly in cases of complete response (endoscopy + biopsy). Little information is available about the follow-up of these patients. We studied long-term results of 35 patients who underwent resection after complete response to pre-operative chemoradiotherapy.

Patients and methods: One hundred and sixty-four patients with resectable carcinoma of the thoracic oesophagus have received the same protocol of CCR (cisplatin 80 mg/m², radiation therapy split course: 37.5 Gy). All patients were followed every 4 months.

Results: Complete response (endoscopy and biopsy) was obtained for 41 patients (25%). Seventeen of them (41.4%) had pathologic complete response (no tumour in the specimen: Group 1). Twenty-four have microsopic foci of residual tumour (Group 2: 58.5%). The overall 3-year survival rate for Group 1 was 49.8% for the whole group (median survival 64 months), 68% for the Group 1 (no tumour in the specimen), 36% for the Group 2 (microscopic focus without residual tumour) (NS).

Conclusions: One half of the complete responses (endoscopies + biopsies) have not a pathologic complete response (microscopic foci of residual tumour in the specimen). The 49.8% 3 year survival suggests a benefit from oesophagectomy for complete response after combined chemoradiotherapy.

42. A risk score for predicting outcome in patients with gastric cancer

M. Victorzon, J. Lundin, C. Huglund, S. Nordling*, P. J. Roberts
Fourth Department of Surgery and *Department of Pathology, Helsinki University Central Hospital, Helsinki, Finland

Twelve variables were studied for possible prognostic value in 242 patients with adenocarcinoma of the stomach. Eight of these had a statistically significant effect on survival in univariate analyses. A multivariate analysis of 196 patients showed that the most significant differences in survival could be explained by three independent variables acting simultaneously, namely stage of disease, Sialyl Tn antigen expression and aneuploidy of the tumour cells. By adding scores for stage (1-4 points), Sialyl Tn expression (0-1 points) and ploidy (0-1 points) a risk score based on these three variables defined the patients into six different risk groups with statistically highly significant differences in survival (χ²=107.74, df = 1, P<0.0001). Application of the risk score improves the prediction of outcome, may help in choosing patients for different treatment modalities, and allows more accurate stratification in clinical trials.

43. The influence of histomorphologic parameters on the lymph node involvement in gastric carcinoma and the significance of systematic D1-D2 lymphadenectomy

W. M. Padberg, U. Doerr, J. Bühr, K. H. Berghofer, C. Kelm
Dept of General and Thoracic Surgery, University of Giessen, Germany

In a retrospective study of 157 patients undergoing a curative resection of a gastric carcinoma between 1982 and 1992 the correlation of the lymph node status and histomorphologic parameters of the gastric cancer and the significance of the systematic lymphadenectomy were analysed. The patients were divided into two groups (exclusively D1- and systematic D1-D2-lymphadenectomy). Among the histomorphologic parameters only the depth of infiltration (pT) revealed a high correlation with the extent of metastatic lymph node involvement. Tumour form, Lauren-classification and tumour localization only showed a marginal influence on the nodal status. The overall 5-year survival rate was not significantly changed by the systematic lymphadenectomy; only the subgroup of the UICC-stadium II demonstrated tumour localization only showed a marginal influence on the nodal status.

In conclusion, the indication for systematic lymphadenectomy; only the subgroup of the UICC-stadium II demonstrated tumour localization only showed a marginal influence on the nodal status. The overall 5-year survival rate was not significantly changed by systematic lymphadenectomy; only the subgroup of the UICC-stadium II demonstrated a high correlation with the extent of metastatic lymph node involvement. Tumour form, Lauren-classification and tumour localization only showed a marginal influence on the nodal status.

44. Prognostic factors for gastric cancer in the Dutch Gastric Cancer Trial

J. J. Bonenkamp, I. Songue, C. J. H. Van de Velden
Dept of Surgery, Kendedor Gastroenterologists, Locatie Elisabeth, Postbus 417, 2000 AK Hauwert, The Netherlands

The depth of gastric wall infiltration, lymph node involvement and distant metastases are the most commonly used prognostic factors for gastric cancer. Surgery is the only option for curative treatment but even after macroscopic curative (R0) resection 5-year survival is less than 30%, often because of early recurrence of (non-detected) distant metastases. Using the database of the prospective randomized Dutch Gastric Cancer Trial, we have studied prognostic factors not yet commonly used in order to improve the detection of non-curable disease.

Pre-operative cytological examination of abdominal washing revealed free tumour cells in 20 of 457 studied patients (4%). Only one of the cytology-positive patients survived longer than 2 years, whereas 3-year survival in those with negative cytology was 29%. Involvement of distant lymph nodes on frozen section of the organ with these cells determines the often significantly decreased expected 3-year survival from 76% to 10%. Failure to achieve free resection lines was also associated with an unfavourable prognosis. Three year survival was 6% when free resection lines were obtained, but decreased to approximately 20% for those with non-radical resection.

At laparotomy for gastric cancer, optimal staging should include cytological examination of abdominal washing, distant lymph node biopsy and frozen section analysis of resection lines. Only these cases without extended tumour infiltration are candidates for curative surgery and should be classified as such. Whether these patients should be treated with extended (D2) lymph node dissection remains a matter of debate until the final results of the Dutch and the British Gastric Cancer Trials will be available.

45. Functional staging in gastric cancer—new aspects through bone marrow micrometastases and tumour-associated proteases

Dept of Surgery, Klinikum Grosshadern, *Institute of Pathology, Ludwig Maximilians University, D-81377 Munich, Germany

The approach towards solid tumours has changed largely by new aspects of tumorgenesis and progress. The detection of early tumour cell dissemination indicated the systemic character of the local gastric cancer. The relationship of the organism with these cells determines the often unpredictable course of an individual tumour after presumed curative primary treatment (Nature Med 1995; 1: 1035-1039). In this context, the prognostic impact of the tumour-associated proteases uPA might be of tumour-related locost impact. However, the role of the uPA system with interactive proteases and inhibitors has to be considered.

In a prospective study of 203 patients with resectable gastric cancer, the detection of disseminated tumour cells in bone marrow performance of immunohistochemically. The expression of activators (plasminogen, collagenase 4, cathepsin D, alpha1-antitrypsin and inhibitors (alpha2-antiplasmin, alpha2-macroglobulin, antithrombin 3, uPA, uPA-R) in the bone marrow micrometastases and tumour-associated proteases. Prognostic Cox analysis performed to correct these results for the relative impact of the uPA system and conventional prognostic factors showed PAI-1 (disease free survival: P=0.002, rel. risk 1.80) overall survival (P=0.0042), alpha2-macroglobulin (P=0.0381) and antithrombin (P=0.0372) with prognostic. Multivariate Cox analysis performed to correct these results for the relative impact of the uPA system and conventional prognostic factors showed PAI-1 (disease free survival: P=0.002, rel. risk 1.80) overall survival (P=0.0042), alpha2-macroglobulin (P=0.0381) and antithrombin (P=0.0372) with prognostic. Multivariate Cox analysis performed to correct these results for the relative impact of the uPA system and conventional prognostic factors showed PAI-1 (disease free survival: P=0.002, rel. risk 1.80) overall survival (P=0.0042), alpha2-macroglobulin (P=0.0381) and antithrombin (P=0.0372) with prognostic. Multivariate Cox analysis performed to correct these results for the relative impact of the uPA system and conventional prognostic factors showed PAI-1 (disease free survival: P=0.002, rel. risk 1.80) overall survival (P=0.0042), alpha2-macroglobulin (P=0.0381) and antithrombin (P=0.0372) with prognostic. Multivariate Cox analysis performed to correct these results for the relative impact of the uPA system and conventional prognostic factors showed PAI-1 (disease free survival: P=0.002, rel. risk 1.80) overall survival (P=0.0042), alpha2-macroglobulin (P=0.0381) and antithrombin (P=0.0372) with prognostic.
47. A randomised trial comparing adjuvant 5-fluorouracil, epirubicin, and mitomycin C (FEM) with no treatment (GC) for increased survival in the subgroup of patients with grade III tumours is feasible and less toxicity than 5-FU bolus therapy. Patients with advanced gastric cancer were treated in a disease-oriented phase II study. 

### Treatment:

- **FA**: 500 mg/m², 2 h infusion d 1, 8, 15, 22, 29, 36, 5-FU 2000 mg/m², 24 h infusion d 1, 8, 15, 22, 29, 36, C 50 mg/m², 1 h infusion d 1, 15, 29, repetition at 50. Depending on response and toxicity up to six cycles were planned.

### Toxicity:

- grade: leucocytes 2.6%, grade: nausea/vomiting 2.5%, grade: mucositis/stomatitis 2%, grade: alopecia 2.10%, grade: 0%

### Conclusion:

- HD-FU/FA/C with continuous infusion is an active regimen for gastric cancer with possibility of 5-year survival, not reaching statistical significance, and remains therefore applicable in an investigational setting. Based on the above data we studied adjuvant CT with 5-FU in randomised study in completely resected stage III GC. CT was started 2-3 weeks after the operation. From 8/1988 until 2/1994 84 patients with completely resected tumours and lymph nodes (LN) were randomised to FEM (group A) vs no treatment (group B). Patients were eligible for randomization if they had KPS $\geq$ 60, no evidence of residual gross cancer, no severe cardiotoxicity, and normal cardiac function. Forty-two patients were randomized in each arm and had no significant differences regarding distribution of age: group A = 53 (31-65) vs group B = 43 (35-64), sex: group A = 32/21 (men/women) vs group B = 29/37 (men/women), site of primary: group A = 22/29 (pylorus or antrum/body) vs group B = 25/17 (pylorus or antrum/body), histologic grade: group A = 0/19/23 (grade I/II/III) vs group B = 0/17/17 (grade I/II/III), LN metastasis: group A = 40 of 42 vs group B = 4 of 22, and surgical procedure: group A = 33% (total gastrectomy/partial gastrectomy/spleenectomy) vs group B = 37/7 (total gastrectomy/partial gastrectomy/spleenectomy). Group A received 5-FU 600 mg/m² i.v. days 1, 8, 29, 36, 45, and mitomycin-C 10 mg/m² day 1.

The schedule was repeated every 56 days for three cycles. Group B received no treatment and was only subjected to the regular follow-up. At last follow-up of 66 months 27/42 patients in group A (64%) have relapsed or died compared to 34/42 patients in group B (81%). The differences in relapse rate and disease free and overall survival were not statistically significant. The subgroup of patients with grade III tumours receiving adjuvant FEM demonstrated a trend towards improved survival ($P=0.085$). Main therapy-related toxicities for the treatment group were: Grade I-III anemia/neutropenia/thrombocytopenia in 16/45/22% of patients, respectively, and grade I-II nausea/vomiting in 29% of patients.

48. Cancer risk in Crohn's disease

G. Timmermanns, G. Schlämm, Ch. Fritz, Ch. Herfarth

Dept of Surgery, University, Heidelberg, Germany

We assessed the cancer risk in Crohn's disease (CD) in a large single centre series. The cancer risk may be increased in CD as observed in ulcerative colitis or other inflammatory diseases due to long-term intestinal inflammation with consecutive up-regulation of chronic epithelial repair mechanisms (including genomic alterations). Epidemiologic data based on cohort studies and biologic data obtained by the analysis of surgically resected specimens is supposed to provide reliable data.

Of 879 surgical patients with CD treated in our department we found 126 patients with cancer. In two of these the diagnosis of carcinoma was known preoperatively. Cancer locations were: colon n = 4, small bowel n = 1, anastomotic region after ileocolonic resection n = 1, perianal fistula n = 1, cloacogenic anal cancer n = 1.

The incidence of small bowel cancer was 14 times higher than expected (ratio observed/expected = 1.0/0.071) whereas the relative colon cancer risk was not increased in these patients (4.8/8.77). Additionally epithelial dysplasia was found in two CRC patients (overall incidence of 1.0 or 2.4% (18/789)). Mean duration of illness was 8.8 years (range 0-14 years), comparable to patients without cancer. The age at the time of diagnosis (40; 23-58 years) was higher in patients with cancer than the mean age of patients without cancer (33; 13-80 years).

The analysis of 240 cases of CD associated carcinoma in the literature revealed a 10 to 80 times increased cancer risk for small bowel cancer as confirmed by our results. The data for colon cancer is controversial with a reported increased cancer risk of up to seven times.

Probable risk factors are dysplasia and DNA-anaploidia, possible risk factors for small bowel carcinoma are long-term history of disease and juvenile onset of disease.

In surgical patients CD is associated with an increased small bowel cancer risk. Further studies should aim to define subgroups of patients who would benefit from a cancer screening program.

49. The role of surgery in the treatment of AIDS-associated gastrointestinal lymphomas

S. Piranse, E. Morandi, A. Ridolfo, C. Valli, S. Sautambrogio, A. Bastagli and V. Rossi

Salvatore Piranne MD, University of Milano, Department of Surgery. L. Sacco Hospital v. G.B. Grassi, 74 20155 Milano, Italy

Introduction: Lymphoma is a relatively late manifestation of the human immunodeficiency virus (HIV) and commonly, in patients with Acquired Immune Deficiency Syndrome (AIDS), presents primary gastrointestinal tract involvement. The optimal treatment of G.I. lymphomas is controversial and the role of surgery is discussed except for emergency operations treating complications as perforation, intestine obstruction or haemorrhage. We present here our multidisciplinary experience in the treatment of primary G.I. lymphomas in AIDS patients.

Patients and methods: From 1987 to 1995, 1205 patients with AIDS were observed at L. Sacco Hospital (Department of Infectious diseases and Department of general surgery). Fifty per cent of these patients had a diagnosis of N.H. lymphoma (4.6%) and 11 of primary G.I. lymphoma (19.6%). All patients were men with mean age of 42 years (range 24-76). The mean duration of HIV seropositivity was 6.3 years (range 2-10). Eight patients had a previous history of opportunistic infections: three patients had cytomegalovirus (CMV) infection, two pneumocystis carinii pneumonia, two mycobacterial infection and one had diffuse candidiasis. Patients has been divided in two groups, A (not surgically treated, five patients) and B (surgically treated, six patients). T-cell (CD-4) count was similar in both groups; 44.4 of mean (range 8-76) and 44.3 of mean (range 16-76) respectively.

Results: One patient was admitted with haematemesis and melena due to haemorrhagic gastric lymphoma and died 15 days later. Another patient with disseminated G.I. lymphoma was treated by a single cycle of chemotherapy but died 30 days later from a mesenteric infarct. Two patients with gastric lymphoma were treated with chemotherapy but died lately for gastric haemorrhage and CMV pneumonia. One patient survived 2 months and the other the 6 months. One patient with primary rectal lymphoma was treated with chemotherapy and local radiotherapy and survived 8 months. In the B group one patient was operated on emergency for peritonitis due to ileal perforation and treated by ileal resection and reanastomosis. Three patients had a subtotal gastrectomy with Roux-en-Y reconstruction for gastric localization. Two patients had a right colectomy for colic infiltration by lymphoma. Post-operative complications occurred in three patients and were pneumonia in one, diarrhea with persistent hypotension in two. However there were no post-operative deaths. Two patients were alive after 10 months and 6 months from operation while the others died after 5 months, 3 months, 6 months and 9 months from surgery.

Conclusions: Today HIV-seropositive patients survive more than in the past, consequently they are at greater risk of G.I. lymphoma. Chemotherapy and radiotherapy are largely used in the treatment of N.H. lymphomas. Nevertheless this therapy worsens the immunodeficiency in AIDS patients. Complications that require emergency abdominal surgery are frequent in G.I. lymphomas but are followed by a prohibitive post-operative mortality rate. Early diagnosis and surgical treatment may give the best chances in the treatment of AIDS-associated gastrointestinal lymphomas.
50. Treatment of peritoneal carcinomatosis: feasibility and primary results
Institut Paoli-Calmettes, 232 Bd Sainte Marguerite, Marseille Cedex 9, France
Between October 1994 and December 1995, 12 patients (sex ratio: 1, median age: 55 (range: 30-66) years) were treated for peritoneal carcinomatosis by combined extensive surgery and aggressive regional chemotherapy. The origin of peritoneal carcinomatosis was as follows: colorectal cancer (n = 8); mulleroblastoma (n = 1); fallopian tube cancer (n = 1); malignant mesotheliomas (n = 1) and malignant pseudomyxoma (n = 1). Two patients had bowel obstruction. For cytoreductive surgery and removal of metastases, peritoneal washings were performed and implants were resected for histological examination and or cytological examination. Residual disease after cytoreductive surgery was less than 3 mm in diameter in six cases and between 3 to 10 mm in diameter in other cases. The mean duration of surgery procedure was 8 hours (ranges 5-11) and mean transfusion performed by three red cell packs (range 0-6). Before starting intra-abdominal chemotherapy, abdominal lavage were performed to obtain fluid clear of blood. Five closed suction type of drains were used to administer intra-abdominal chemotherapy as follows: chemotherapy instillation 1 hour in a large volume of fluid (800 ml) in 50 ml/min for patients with ascites, chemotherapy instillation 2 hours for patients without ascites. Two different protocols were used for intra-abdominal chemotherapy: (1) mitomycin C, day 1, 10 mg/m2 and 5-fluouracil day 2 to 5; 15 mg/kg for 10 patients and (2) doxorubicin 0.1 mg/kg and cisplatinum 15 mg/m2 day 1 to 5 for two patients (mulleroblastoma and meseotheloma). The postoperative mortality rate was 0% and mean hospital stay was 28 days (range 18-80). The postoperative morbidity was as follows: (1) intra-abdominal diseases: bowel perforations (n=2) and bleeding (n=1) which required three relaparotomies, one patient drained under sonography. (2) general complications: infectious diseases (n=4) and short bowel syndrome (n=1). The mean post-operative ileus was 8 days (range 6-19). Pre-operative bowel obstruction and extensive bowel resection increased post-operative morbidity rate. One patient died at 6 months for chest and hepatic metastases. The follow-up was: (1) two patients alove up than one year without carcinomatosis recurrence but one with hepatic metastasis. (2) Nine patients alive less than one year, none with carcinomatosis recurrence. For selected patients (without extra-abdominal metastasis or preoperative bowel obstruction), extensive cytoreductive surgery with visceral resections in some cases and immediate intra-abdominal chemotherapy could allowed acceptable survival without prohibitive morbidity in a disease for which untreated prognosis is only 6 months survival.

51. MR-guided laparoscopy: technique and perspectives in abdominal malignancies
Division of Visceral Surgery, Department of Surgery, University of Zurich Hospital and Department of Radiology*, University of Zurich Hospital, Zurich, Switzerland
Aim of the study: The main disadvantage of conventional laparoscopy is the lack of a true 3D view. An experimental study has been initiated to evaluate the use of MR-guidance during laparoscopy. Materials and methods: Using a recently developed open configured MR-system (0.5 Tesla, General Electric) with free admissiteness to the patient (36 cm vertical access), minimal invasive procedures can be done under realtime MR-guidance. In an animal model we evaluated the practicability of laparoscopy in the MR environment. Results: Eight pigs (female, body weight 35-40 kg) underwent MR-guided laparoscopy. Technical equipment has been placed outside of the magnetic field to reach all exposed surfaces. Drains remained for 24 hours during 5 days. Two different protocols were used for intra-abdominal chemotherapy: (1) mitomycin C, day 1, 10 mg/m2 and 5-fluouracil day 2 to 5; 15 mg/kg for 10 patients and (2) doxorubicin 0.1 mg/kg and cisplatinum 15 mg/m2 day 1 to 5 for two patients (mulleroblastoma and mesotheloma). The postoperative mortality rate was 0% and mean hospital stay was 28 days (range 18-80). The postoperative morbidity was as follows: (1) intra-abdominal diseases: bowel perforations (n=2) and bleeding (n=1) which required three relaparotomies, one patient drained under sonography. (2) general complications: infectious diseases (n=4) and short bowel syndrome (n=1). The mean post-operative ileus was 8 days (range 6-19). Pre-operative bowel obstruction and extensive bowel resection increased post-operative morbidity rate. One patient died at 6 months for chest and hepatic metastases. The follow-up was: (1) two patients alove up than one year without carcinomatosis recurrence but one with hepatic metastasis. (2) Nine patients alive less than one year, none with carcinomatosis recurrence. For selected patients (without extra-abdominal metastasis or preoperative bowel obstruction), extensive cytoreductive surgery with visceral resections in some cases and immediate intra-abdominal chemotherapy could allowed acceptable survival without prohibitive morbidity in a disease for which untreated prognosis is only 6 months survival.

52. Surgically directed intraperitoneal heated chemotherapy for the treatment and prevention of malignant ascites
B. W. Loggie, M. Perini, R. A. Fleming, G. B. Russell, and K. Geisinger
Bowman Gray School of Medicine, Woke Forest University, Winston-Salem, NC, USA 27117
No standard effective therapy exists for the treatment of malignant ascites (MA) associated with non-ovarian peritoneal carcinomatosis (PC). Quality of life is poor for these unfortunate patients (pts) with median survival typically less than 6 months. A clinical trial of cytoreductive surgery combined with intraperitoneal heated chemotherapy perfusion (CS + IPHC) in pts with disseminated IPPC is presented.

Methods and results: Pts with histologically proven PC were explored and underwent radical surgical debulking followed by a 2-hour heated perfusion with mitomycin C. Presence of ascites was documented at surgery. Cytology was examined pre- and post-IPHC. Pts were followed at 3-month intervals. Survival was calculated by Kaplan-Meier analysis. Thirty-four pts were treated (15 f, 19 m), median age 53 (17-76). Most (80%) had tumours of gastrointestinal origin (colon 14, appendix eight, stomach, four, other, eight). Prior therapy included surgery (n = 29, 39%) or chemotherapy (n = 20, 59%). Frank ascites was present in 12 pts (Group A, 35%), malignant IP cytology without gross ascites was present in another 12 (Group B, 33%), and neither in 10 (Group C, 29%). CS + IPHC took median 8.4 hours (5-14 h) with R2 resection status in 78%. There were no operative deaths and median discharge was 14 days (10-22). The overall survival at 1, 2, and 3 years was 92%, 71%, and 54%, respectively.

Discussion: Malignant ascites was controlled or prevented in the majority of pts. CS + IPHC is relatively well-tolerated and may improve survival in pts with PC.

53. Laparoscopy promotes intraperitoneal tumour growth in an animal model
H. R. Dorrance, K. Oein*, P. J. O'Dwyer
Dept of Surgery, *Dept Pathology, Western Infirmary, Glasgow, UK
The effect of laparoscopy on cancer spread is poorly understood. The aim of this study was to assess the effect of a carbon dioxide (CO2) and helium pneumoperitoneum on tumour growth and metastases in an animal model.

Under general anaesthesia and in separate experiments female F344 rats were given an intraperitoneal or tail vein injection of 1 x 107 MTLn3 tumour cells and then randomized into three groups: anaesthetic only (control), CO2 pneumoperitoneum and helium pneumoperitoneum (insufflation pressure 8 mmHg).

<table>
<thead>
<tr>
<th>Group</th>
<th>Omental tumour gms</th>
<th>Peritoneal nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4.0 (3.2-5.9)</td>
<td>0 (0-1.0)</td>
</tr>
<tr>
<td>CO2</td>
<td>7.5 (5.8-8.8)</td>
<td>17.0 (10.0-20.0)</td>
</tr>
<tr>
<td>Helium</td>
<td>6.1 (5.0-8.3)</td>
<td>19.5 (12.3-23.7)</td>
</tr>
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</table>

P value* ≤ 0.018

All values medians. *compared with controls using Mann–Whitney U-Wilcoxon Rank Sum Test.

Results: Following tail vein injection of MTLn3 tumour cells, lung metastases occurred with equal frequency (P = n.s.) in control and insufflated groups, median values-control five (3–12), CO2 nine (7-10), helium six (6-14).

This study shows that laparoscopy promotes intraperitoneal tumour growth and spread but has not been controlled in 5% of Group A, with failures at 14, 4, and 1 month. No ascites developed in pts in Group B and C. Median survival was 10.1 mo. in Group A with 39% 1-year and 39% 2-year survival compared with 32.7 mo. (P = 0.013), 90% and 54%, respectively, for Groups B and C combined.

Discussion: Malignant ascites was controlled or prevented in the majority of pts. CS + IPHC is relatively well-tolerated and may improve survival in pts with PC.
To evaluate the efficacy of transrectal ultrasound (TRUS) we retrospectively reviewed 150 consecutive patients all of whom had biopsy at time of TRUS. Patients underwent TRUS biopsy for either palpable suspicious nodules or elevated prostate specific antigen (PSA). Fifteen percent of transrectal ultrasound examination demonstrated a suspicious lesion. However, 95% of these lesions were positive for cancer on biopsy. Eighty-five percent of transrectal ultrasound showed no suspicious lesions but 25% of these demonstrated the presence of carcinoma.

It would therefore appear that the sensitivity of transrectal ultrasound is poor and that a significant number of carcinomas would be missed in the absence of biopsy. We therefore believe that the primary role of transrectal ultrasound is for needle guided prostatic biopsy and that TRUS without biopsy has no place in the assessment of patients with a suspicion of underlying malignancy.

57. Laparoscopic para-aortic lymphadenectomy in the lateral position in cancer patients

E. Steckle, R. Gaston

Department of Surgery, Institut Bergonié, Regional Cancer Center, 180, rue de Saint-Gémes, 33476 Bordeaux Cedex, France

A technique of laparoscopic para-aortic lymphadenectomy in the lateral position permitting easy mobilization of the intestines without the use of a retractor is described. From March 1995 to January 1996 ten patients (pts) were operated. The procedure was performed eight times in the left position and twice in the right position. Lymphadenectomy was complete in four pts, partial in six pts with fixed nodes. Haemorrhage (500 ml) occurred in one pt. Conversion to laparotomy was not necessary. Mean post-operative stay was 3 days (extremes 2-8 days) and was uneventful in nine patients. One patient developed a large subcutaneous emphysema post-operatively which regressed spontaneously. The indications for the procedure were diagnostic in one case (a Hodgkin's disease was found to the woman) and therapeutic in the nine cases of testicular cancers. Chemotherapy was stopped because of negative findings in seven patients (confirmed by two thoracotomies, one pre-operatively) and continued in two patients with positive findings. This technique could be applied as a diagnostic or a follow-up procedure in various cancers even in obese pts because of the good exposure of the retroperitoneal space in the lateral position.

58. Gracilis muscle flap in the treatment of persistent pelvic infection

Th. Wiggers, I. H. M. Borle Rinkes

Department of Surgical Oncology, University Hospital Rotterdam/Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

The occurrence of persistent pelvic infection following extensive surgery and radiotherapy is infrequent but difficult to treat. In most cases the omentum is already used for induction of healing and obliteration of dead space after extensive surgery and radiotherapy: An initial experience with the use of a gracilis muscle flap is described.

Patients and methods: Seven consecutive patients with persistent pelvic infection (five men and two women) were studied (median time from completion of evidence and infection 6 months). Multiple biopsies were performed to exclude recurrent tumour growth. Patients were operated in jack-knife position and the gracilis muscle was mobilized after a medial longitudinal incision. A subcutaneous tunnel was created over the ischial tuberosity to reach the pelvic area. The muscle was fixed with 2-3 absorbable sutures.

Results: Median operating time was 90 minutes. Post-operative morbidity was low (one superficial wound infection). Six out of seven patients were cured with a median time of 5 months. One patient developed again an infection and finally proved to have recurrent disease.
59. Lymph node metastases in head and neck cancer: node yield in dissection of fresh tissue

Department of Oral Pathology, Dublin Dental Hospital, and Departments of Pathology, Otolaryngology/Head and Neck Surgery, Haematology and Oncology, St James's Hospital, Dublin

What constitutes an adequate or ideal node yield in lymph node resections for head and neck cancer is not clearly established. A detailed examination of neck dissections and paratracheal tissue was performed documenting numbers, size and gross appearance of lymph nodes in the fresh state. Of 76 neck dissections received, 41 were tumour free, 20 cases included paratracheal nodes. The average node yield from radical/modified radical neck dissections was 34 (range 10-62), selective/supraomohyoid neck 12.9 (range 3-23) and paratracheal nodes 11.8 (range 1-30). In the tumour-positive necks, 140 (90%) of 155 nodes contained tumour. There were 61 positive nodes (43%) measuring <1 cm, of which 37 appeared grossly negative on gross examination. Twenty positive nodes (14%) were >0.5 cm. Extracapsular spread was present in 41 positive nodes (28%), nine of which were <1 cm. Five of these nine appeared grossly negative for tumour. The finding of small positive lymph nodes in head and neck resections is common, with many appearing innocent on gross inspection. Their documentation by thorough examination of nodal tissue is necessary to address the issue of whether they can carry the same implications as larger positive nodes.

60. Interest of surgery-brachytherapy association in the treatment of epidermoid cancers of the floor of mouth

Unite de Chirurgie Cervico-Faciale. Centre Alexis Vautrin 54511 Itandoeuvre Les Nancy Cedex, France

This is a retrospective study of two groups of patients treated by surgery for epidermoid carcinomas of the floor of mouth. The first group included patients at high risk of recurrence (margins at risk) for whom a post-operative irradiation always involved brachytherapy, and the second group included patients at low risk of recurrence for whom post-operative irradiation was limited to an exclusive external beam irradiation. Our aim was to determine the benefit of a boost to the surgical scar delivered by post-operative brachytherapy.

Material and methods: The study lasted from 1979 until 1992. Two groups of 32 and 36 patients presenting an epidermoid carcinoma of the floor of mouth received first line surgery. The first group of 32 patients (12 T1-T2; 20 T3-T4-Tx) received low dose rate brachytherapy using Iridium 192 after surgical resection of the tumour because of invaded margins or considered at risk (<5 mm). Brachytherapy was delivered in 1 or 2 planes to the surgical scar. In case of suture too close to the mandibular area, a bridge technique was used. In this group of patients, 20 received an external radiotherapy. The mean dose delivered by brachytherapy was 57 Gy in cases of exclusive brachytherapy and 22 Gy in cases of brachytherapy combined with an external beam irradiation (dose to the surgical scar: 50 Gy).

The second group included 36 patients (12 T1-T2; 24 T3-T4-Tx) for whom surgical resection of the tumour was satisfactory. The mean dose delivered by exclusive external beam irradiation was 50 Gy.

The two groups were comparable for all factors (age, sex, stage, surgical technique . . .) except for resection margins.

Results: The mean follow-up was 36 months (from 5 to 145). The results at 5 years were as follows in the groups treated by brachytherapy and exclusive external beam irradiation respectively:

- overall survival: 62 and 43% calculated by the Kaplan-Meyer method
- specific survival: 74 and 53%
- local control: 80 and 60% (P = 0.09), (log rank)
- severe complications: 4/32 and 1/36.

Conclusions: A post-operative brachytherapy with a boost to the surgical scar allows better local control in patients presenting resection margins at risk, compared to patients whose resection margins were considered as satisfactory. These good results are encouraging and should allow improvements with the use of new techniques of brachytherapy. Low dose rate pre-operative brachytherapy in tubes or high dose rate pre-operative brachytherapy delivering a high dose in one session and allowing an immediate reconstruction without irradiating transferred tissues may be appropriate.

61. Surgical treatment and long-term survival rate in patients with papillary thyroid carcinoma

Institute of Oncology and Radiology of Serbia, Belgrade, Yugoslavia

Papillary thyroid carcinoma (PTC) is the most frequent thyroid cancer. Important prognostic factors of survival in patients with PTC are: age of the patients at diagnosis, sex, size of tumour, histological grading, stage of disease (TNM) and surgical treatment. Prognostic factors in PTC are often analysed together.

The aim of our study was to analyse a long-term survival rate in patients with PTC according to prognostic factors. From January 1981 to January 1996, there were 128 patients surgically treated due to papillary thyroid carcinoma (PTC). Total thyroidectomy (TT) was undertaken in 120 patients—T1 with TT + dissection of the central and lower jugular lymph nodes for frozen-section histopathology of these. 71.43% (85 patients), with metastatic lymph nodes (MLN), were surgically treated with modified radical neck dissection (MRND). Palliative and diagnostic surgery of advanced cancer was carried out in eight cases. External radiotherapy was applied in 16 and 1º in 28 patients. Age: 42 ± 15.2 (median 40 and range 8-88). Sex ratio—Female (F):Male (M) = 2.66:1. Survival analysis: Kaplan-Meier, Log Rank, Wilcoxon test.

Long-term survival rate in our group reach 84.48% at 15 years follow-up. We followed the survival rate according to prognostic factors: age at diagnosis (≤45 and >45: P = 8.43 x 10^-5), sex (F-M), presence of initial distant metastasis (P = 0.015), extracapsular tumour, initial lymph node metastasises itself and correlate with age at diagnosis (≤45 and >45 = P = 0.0008), and sex-female (F) + age ≤45 and >45 (P = 0.002). According to surgical treatment and presence of MLN in frozen-section examination, two groups of patients were selected. Group A (TT with positive MLN + MRND) and group B (TT without MLN in paratracheal lymph nodes). Long-term survival rate at 10 years reach 93.22% in group A and 79.21% in group B (P = 0.067). In correlation with age at diagnosis, group A was divided to subgroups: A1 (≤45) and A2 (>45). Ten years survival rate in A1 is almost (100%) vs A2 with 77.3% (P = 0.002).

In addition to known prognostic factors, surgical treatment in group A, could have same impact on survival rate of this patients.

Key words: papillary thyroid carcinoma; surgical treatment.

62. Post-operative complications after completion thyroidectomy for different rates thyroid carcinoma

L. Pazzullo, P. Delrio, F. Ionna, V. Formisano
Division of Surgical Oncology, Head of Division. N. Moccia, National Cancer Institute, Naples, Italy

Surgical approach in thyroid carcinoma is still controversial: many authors consider it necessary to remove the whole gland and completion thyroidectomy (CT) is therefore sometimes required. Main indications are follicular cancer or patients with 1 cm or greater carcinoma treated with lobectomy or limited resection (early CTI, local recurrence after previous treatment (late CT). Several authors, on the contrary, indicate high rate of complications for completion thyroidectomy and advocate its use in limited circumstances.

Patients and methods: In order to evaluate the results of our completion thyroidectomies we reviewed the medical records of all patients who underwent CT for thyroid cancer in our division since 1990 to 1995. All information about initial operation, time of re-operation, cancer in the residual gland and post-operative complications were recorded.

Results: Out of 131 patients treated for thyroid cancer 35 (26.7%) received a completion thyroidectomy for papillary thyroid carcinoma. Re-operation was performed within 6 months in 26 cases (74.3%) and later in the remaining nine cases (25.7%). Of the early CT group 16 patients (45.7%) were previously operated in other surgical units and 10 patients (28.5%) had received primary treatment in our institution. None of the patients had received previous irradiation of the neck region. Local recurrence of the disease was the indication to surgery in the nine late CT patients (2.8%). Immediate reconstruction without irradiating transferred tissues may be appropriate.

Abstracts

Head and neck
risk patients (5.3–14.3%) were the indications to the early CT performed. Carcinoma in the residual gland was found in four cases of papillary cancer (11.4%), in three cases of follicular cancer (8.5%) and in two high risk patients with small thyroid gland (5.6%). Recurrent laryngeal paralysis occurred in one patient (2.8%). Transient hypoparathyroidism was evident in two patients (5.6%) and became permanent in one case (2.8%).

Discussion: Removal of the thyroid gland seems to be the most appropriate treatment for thyroid cancer in most cases. Limited resections do not guarantee oncologic radicality due to the high rate of multifocality both for papillary and follicular cancer. Completion thyroidectomy is therefore necessary in cases where local control is unsatisfactory and in those patients with local recurrence and distant metastases. CT allows radioiodine therapy after surgery. Despite the known difficulties in re-operating on a previously treated neck, we believe that with a correct surgical approach morbidity is minimal and adequate treatment can be achieved.

63. Surgery with adjuvant radiotherapy improves local control but not survival for advanced salivary carcinomas

A. Renehan1, M. McGurk2, E. N. Gleave1
1University Department of Surgery, University Hospital of South Manchester, West Didsbury, Manchester, M20 8LR, UK, 2Department of Oral & Maxillofacial Surg (UMDS). London, UK

Several studies have shown the efficacy of post-operative radiotherapy in improving local control in patients with advanced salivary carcinoma but its influence on long-term survival is controversial. Between 1952 and 1992, 117 patients (parotid; 95; submandibular; 6; minor glands, 16) were treated at the Christie Hospital, Manchester, by either surgery alone, SG (n = 48) or surgery plus radiotherapy, SG + RT (n = 69). Radiation was usually given 4 to 6 weeks after surgery and doses ranged from 3750 to 7200 cGy (median 5000 cGy). Treatment outcome was assessed according to TNM (UICC) tumour size; T1/T2 (n = 61) and T3/T4 (n = 56). Loco-regional control was improved by SG + RT compared to surgery alone in the T3/T4 tumour group (76% vs 37%, P = 0.005). The 10-year determinate survival rates for patients given SG + RT vs SG with T1/T2 tumours were 91% vs 90% (P = 0.64) and for T3/T4 tumours were 50% vs 41% (P = 0.21). Using the Cox Model, multivariate analysis revealed that tumour size (Relative Risk = 1.99, P = 0.001) and the use of adjuvant radiotherapy (negative coefficient, RR = 0.42, P = 0.02) were the most important factors affecting loco-regional control. Although the incidence of distant metastases (13.5%) and secondary primary tumours (4.3%) was high, the effect of radiotherapy on survival was small (5-year survival difference of 6%).

64. Multimodality treatment of anaplastic thyroid cancer

G. Pély1, I. Besznyák
Department of Surgery, National Institute of Oncology, Budapest

Of the 506 patients who underwent surgery for thyroid malignancy at the Department of Surgery, National Cancer Institute, Budapest, Hungary between 1977 and 1995, 44 had anaplastic cancer. Clinical data of these patients are reviewed and our results in the treatment of this highly malignant disease are discussed. A rapidly growing neck mass, compressive symptoms, locally advanced and disseminated disease, pre-existing goitre and age of 50 years or older were the main clinical characteristics of our patients. Surgery with curative intent was possible in 64% of our patients while biopsy or tumour debulking was performed in the remaining 36%. Extension of surgery towards the vital structures of the neck in cases of anaplastic thyroid cancer is not recommended. Of the 44 patients 27 received post-operative treatment. As a benefit of multimodality treatment local control was achieved in 20 patients who underwent curative surgery. Survival was 43% at six months, 30% at one year and 7% at two years after surgery. Only one patient survived longer than five years.

We conclude that despite multidisciplinary treatment anaplastic thyroid cancer still remains a highly fatal disease. Surgery—if feasible—is the most effective palliative treatment at present.

65. Technique, morbidity and results of reconstruction after extensive laryngopharyngeal resection

The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

Between 1984 and 1994 a total laryngectomy in combination with a near-total pharyngectomy (the latter with or without oesophagectomy) was performed in 34 patients for resection of a carcinoma. Three different reconstruction techniques were used, dependent on the extent of the surgical defect. In cases of a near-total pharyngectomy, leaving a narrow strip of pharyngeal mucosa, a pectoralis major myocutaneous flap (9) was used. If a circumferential defect without oesophagectomy was created, a free revascularized jejunal segment (9) was applied. If an oesophagectomy was necessary as well, a total stomach (6) or a tubed stomach reconstruction (10) was used. An indwelling Provox® voice prosthesis was applied primarily in all cases except after reconstructions using the stomach where secondary puncture was preferred.

In the group with the oesophagectomy a higher number and more serious complications occurred due to the greater extent of the resection performed. Two patients with a total gastric pull-up died in the post-operative period. Two patients in the tubed stomach group encountered partial necrosis of the stomach. Other serious complications included anaesthetic leakage (5), chyle leakage (3) and pharyngo-gastric stenosis (2). Swallowing function was assessed in 32 patients with a reasonable or good result in 26. Of the 30 patients eligible for speech evaluation 28 achieved a speech quality comparable to that after standard laryngectomy. Survival in this selected patient group was moderate, with a 2-year overall survival of 48% and a 2-year disease free survival of 43%.

It is concluded that the morbidity of these major surgical procedures is considerable. Swallow function and speech quality are satisfactory in the vast majority of these patients.

66. Options for surgical repair for stage 2 and stage 3 squamous cell carcinoma of the oral cavity

M. Prior, M. K. Roy, H. S. Shukla, A. K. Asthana, M. Kumar
Department of Surgery, Institute of Medical Sciences, Banaras Hindu University, India

In Varanasi cancer of the oral cavity accounts for 30–40% of cancers in all sites. While smaller tumours are best treated by local excision and/or radiotherapy, the larger tumours (Stage 2 and above) usually require radiochemotherapy and wide surgical excision in order to obtain adequate local control of the disease. Excision often also necessitates o bicep regional lymph node dissection, with consequent disturbance of local anatomy and function. In this respect, appropriate reconstructive techniques must be employed to restore oral cosmesis and function as far as is possible. In this prospective study 62 patients with oral cancer were treated. They required a wide range of operating techniques for wound closure (Table 1). Of these patients 4.7% (n = 3) died in the immediate post-operative period, 14% (n = 9) were lost to followup, 26.5% (n = 17) developed local recurrence, 3% (n = 2) developed distant disease and 30% (n = 25) remained disease free over the observation period of 2–4 years.

Table 1. Methods of wound closure

<table>
<thead>
<tr>
<th>Wound closure</th>
<th>Number</th>
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<tbody>
<tr>
<td>Primary closure</td>
<td>15</td>
</tr>
<tr>
<td>Forehead flap</td>
<td>12</td>
</tr>
<tr>
<td>Pec. major flap</td>
<td>10</td>
</tr>
<tr>
<td>Bilobed flap</td>
<td>6</td>
</tr>
<tr>
<td>Tongue flap</td>
<td>14</td>
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<tr>
<td>Nasolabial flap</td>
<td>3</td>
</tr>
<tr>
<td>Delto pectoral flap</td>
<td>4</td>
</tr>
<tr>
<td>Split skin graft</td>
<td>10</td>
</tr>
</tbody>
</table>

67. Invasion of the mandible by squamous cell carcinoma of the oral cavity and oropharynx

D. A. Smyth, T. P. O’Dwyen, C. O. Keeney, J. Stack
Departments of Otolaryngology/Head and Neck Surgery, Pathology* and Radiology*, Mater Misericordiae Hospital, Dublin

The overall reported incidence of mandibular invasion by oral cavity tumours is about 20%. The degree of invasion varies from involvement of the
periosteum to frank infiltration of the bone with involvement of cortex alone or through the cortex to medulla. Prediction of the degree of invasion periosteum to medulla and or through the cortex to medulla. Prediction of the degree of invasion periosteum to medulla and or through the cortex to medulla.

69. Surgical therapy of malignant thymomas

K. Thaler, A. Altendorf-Hofmann, R. Schult, W. Hohenberger
Chirurgische Universitatsklinik Erlangen, Krankenhausstr. 12, 91054 Erlangen
Appropriate therapy of malignant tumours of the thymus is surgical removal.

Abstracts

68. Through-and-through oral cancer (T4 +) --- a surgical challenge to answer

L. Postes, M. Ribeiro, L. Santos, M. J. Bastos, C. Sanches, J. L. Fogo, J. G. Santos, G. Dos Santos
Instituto Portugu~s de Oncologia Francisco Gentil, Centro do Porto, Rua Dr Antonio Bernardino de Almeida, 4200 Porto, Portugal

Introduction: Through-and-through oral cancer (T4 +) involving contiguous mucosa, muscle, sometimes bone, and skin is a disease with very poor prognosis in which surgical treatment, even palliative, plays the main role.

Restoration of devastating effects caused by en bloc resection of these tumours represents one of the greatest challenges in head and neck reconstructive surgery.

Patients and methods: Between January 1989 and December 1995, we performed 81 head and neck reconstructions with myocutaneous flaps. 11 of which were full-thickness defects. To repair these defects we have used the following flaps: Pectoralis major myocutaneous flap with flap (2); Trapezius myocutaneous flap with two skin islands--(3); Pectoralis major myocutaneous flap + Trapezius myocutaneous flap--(3); Latissimus dorsi myocutaneous free flap--(1).

Hepato-biliary

70. Surgical treatment of non-colorectal hepatic metastases: long-term results of multicentric retrospective study

G. Lorimer1, F. Lalanne2
1Centre Paul Pupin, 2 rue Moliere, 40033 Angers Cedex 01, France, 2Hopital Tenon, 4 rue du la Chine, 75020 Paris Cedex 01, France

Ninety-one non-colorectal hepatic metastases have been resected between 1976 and 1990, and followed up in a multicentric retrospective study. Hepatic metastases arising from neuro-endocrine tumours were excluded. There were 31 synchronous and 60 metachronous metastases. The most common sites of primary tumour were the stomach (16), the breast (14), the lung (8), the colorectum (7), the kidney (5), the testis (5), the anus (4), the uterus (4), and the oesophagus (2). The most common histopathologic types of primary tumour were adenocarcinoma (42), squamous carcinoma (15) and more rarely sarcoma, teratoma and melanoma. Surgical procedures were single wedge resection (21) and hepatectomy (70). Resection was curative in 76% with safety margins of 1 cm for 60% of the patients. Operative mortality was 1.1% and the morbidity was 11%, represented by seven biliary fistulas, 11 sepsis, and 18 various general complications. Half of the patients underwent adjuvant chemotherapy. The advantage of adjuvant chemotherapy on survival remains uncertain until further investigations are known. Whether neoadjuvant radiation with or without chemotherapy increases the rate of curative resections remains uncertain.

71. Successful treatment of liver metastases by radiolabelled octreotide

G. D. Slooter, W. A. P. Breeman1, E. P. Krenning1, R. L. Marquet, C. H. J. van Eijk
Depart of Surgery and Nuclear Medicine1, Erasmus University, Rotterdam, The Netherlands

Recently we found that the somatostatin analogue octreotide significantly inhibited tumour growth in a rat model of liver metastases. Octreotide was given twice daily, 50 µg/kg s.c. during four weeks after intraperitoneal injection of somatostatin receptor (SS-R) positive pancreatic tumour cells or SS-R negative colon tumour cells. The mean liver weight decreased from 17.9 ± 3.0 g (in controls) to 14.5 ± 3.7 g (P<0.05) in the experimental using the SS-R positive tumour cells. No effect was found on growth and development of the SS-R negative tumour. Octreotide did not influence the levels of growth hormone (GH), prolactin (PRL), and insulin-like growth factor (IGF-1), suggesting that the effect of octreotide was not indirect, but direct and SS-R mediated. Since SS-R on tumours can clinically be demonstrated by radiolabelled octreotide scintigraphy and because radiotherapy with [111In-DTPA-D-Phe10]octreotide shows promising results in a Phase I trial in our hospital, the effect of this Indium labelled octreotide was further developed in our experimental SS-R positive pancreatic tumour model. 370 MBq (0.5 µg) [111In-DTPA-D-Phe10]octreotide was given i.v. on days 1 and 8 following intraportal injection of tumour cells. The control group was given the ligand i.v. but without radiolucence. The number of tumour colonies in the liver was counted after 3 weeks. It was found that the number of colonies in the 'irradiated' group (n=6) was negligible (4 out of 6 negative, one 3 and one
15 colonics), vs 3->100 (median 49) in the control group (n=6). The liver weights were 114.4 and 123.3, respectively (ns). There were no signs of toxicity. These findings confirm our preliminary clinical results and open avenues to improve and refine a promising novel therapeutic approach.

72. Prospective evaluation of Pringle's manoeuvre in hepatectomy for liver cancer—an interim report of a randomized study

K. Man, S. T. Fan
Department of Surgery, The University of Hong Kong, Hong Kong

Background: Pringle's manoeuvre is traditionally used during hepatectomy for liver cancer to reduce blood loss but there is potential harmful effect on the metabolic function of liver cells. Up to now there is no prospective randomized study to document its usefulness. We carried out a prospective randomized study to determine if Pringle's manoeuvre can decrease blood loss during hepatectomy, improve outcome and affect the metabolism of liver cells.

Method: We studied 37 patients who underwent hepatectomy for liver cancer. They were randomly assigned to liver transection with intermittent clamping of 20 minutes and 5 minutes of clamp-free interval (n=19) or liver transection without clamping (n=18). A basal ketone body ratio (AKBR) which reflected hepatic mitochondrial function was measured during the post-operative period.

Results: The two groups were comparable in terms of pre-operative liver function as measured by Indocyanine Green (ICG) clearance test and proportion of patients undergoing major hepatectomy. Pringle's manoeuvre resulted in less blood loss during transection (0.918 ± 0.15 litres vs 2.12 ± 0.59 litres, F = 0.0158), less blood loss in relation to transection raw area (14 ± 2 ml/cm² vs 33 ± 8 ml/cm², F = 0.0310), better AKBR in the first 3 hours after hepatectomy (0.86 ± 0.07 vs 0.57 ± 0.06, F = 0.007) and higher serum transferrin level on post-operative day 1 and 4. The complication rate (5/19 vs 3/18), the mortality rate (1/19 vs 1/18) and the ICG clearance test on post-operative day 8 were the same between the two groups.

Conclusion: Pringle's manoeuvre during hepatectomy resulted in better preservation of liver function in the early post-operative period probably due to less blood loss and haemodynamic disturbance induced by the procedure. More patients will be recruited to validate the result.

73. Role of the E-cadherin cell-cell adhesion complex in liver metastases from colorectal primary tumours

T. J. Hugh, G. J. Poston and A. R. Kinsella
Cellular Oncology Group, Department of Surgery, University of Liverpool, Liverpool, UK

The E-cadherin cell-adhesion complex is made up of E-cadherin, a transmembrane glycoprotein responsible for calcium dependent cell-cell adhesion, and several cytoplasmic proteins a-catenin, b-catenin, and the product of the tumour suppressor gene, APC. Reduced E-cadherin and a-catenin expression have been shown to correlate with de-differentiation in several human tumours. The purpose of this study was to document patterns of expression of the components of the E-cadherin complex in a large series of liver metastases from colorectal primary tumours.

Frozen sections of liver metastases from 51 patients with colorectal primaries were examined for expression of E-cadherin, a-catenin, and b-catenin. These antigens were detected by monoclonal antibodies using standard immunoperoxidase techniques. There were 34 males and 17 females in this series with a median age of 65 years (37-83 years). Two patients underwent repeat liver resections and these specimens were also included. E-cadherin expression was dependent on the type of monoclonal antibody used. HECD-1 (intracellular epitope) identified strong expression in 37/53 (70%) specimens while 6F9 (extracellular epitope) identified similar strong staining in only 26/53 (49%) specimens. Strong expression of a-catenin and b-catenin was seen in 27/53 (51%) and 33/53 (62%) specimens, respectively. Strong expression of all components of the E-cadherin cell adhesion complex was seen in only 10 specimens while there was absent or weak expression of all components in only three specimens. Weak or absent E-cadherin expression in the specimens (10/53) was usually associated with a similar poor expression of a-catenin (7/10) although strong b-catenin expression was seen in many of this group (6/10). This is the first documented evidence of b-catenin expression in liver metastases.

These results are consistent with patterns of expression seen in an unrelated series of primary colorectal cancers studied in our laboratory. We are currently undertaking similar immunochimistical studies on the corresponding primary tumours which led to the liver metastases in this series. Comparisons of expression of the E-cadherin cell adhesion complex in primary colorectal tumours with their expression in the corresponding metastases may lead to a better understanding of the role played by the complex in the development of invasion and metastases. Molecular analysis of the complex is also necessary in order to identify possible mutations in the E-cadherin, a-catenin, and b-catenin genes which may alter the function of the complex.

74. Liver resection index—experience in 400 patients

University of Munich, Klinikum Grosshadern, Department of Surgery and *Department of Medicine, Marchioninistr. 15, D-8177 Munich, Germany

Post-operative hepatic failure is one of the major causes of fatal outcome after liver resection. The aim of the study was to compare the prediction of patient's prognosis by clinical parameters and the liver resection index (LRI) introduced in 1994.

Between October 1990 and March 1996 a total of 400 patients (pts) underwent liver resections in our institution (210 male, 120 female pts, mean age 56.7 years) with a hospital mortality of 3.3% (13400 pts). The indications for operation were metastases from malignant tumours in 218 pts and primary hepatobiliary tumours in 69 pts. Pre-operative 14C-aminoacid breath test (ABT) as measure of liver function was determined. By computer-assisted measurement of CT scans pre-operative liver volumes, tumour volumes and volumes of liver resection as well as the parenchymal hepatic resection rate (PHRR) according to Okamoto were quantified in 250 patients.

Pre-operative volumetric analysis of extent of a planned liver resection and calculation of the liver resection index, a combination of liver function, volumetric and patient parameters is important in the prediction of patients survival with a sensitivity of 75% and a specificity of 83%. Better patient selection and pretreatment by chemoembolization can improve prognosis and post-operative survival in patients at risk for liver failure.

75. Chemoembolization before resection or transplantation for hepatocellular carcinoma (HCC): a relationship between histopathology and disease free survival

E. Akpinaer, H. Bisnuth, R. Adam, D. Castrigna
Hepato-Biliary and Liver Transplantation Center, Paul Brousse Hospital, Villejuif, France

In this report, we aim to present the analysis of recurrence patterns parallel to histopathological findings of cirrhotic patients bearing HCC treated by resection or transplantation after various curves of transcatheter arterial chemoembolizations (TAE).

Patients and methods: Between May 1984 and February 1996, TAE were performed to 735 patients with HCC in our center. Of them, 91 cirrhotic patients were subsequently treated by resection (RES: 47 pts) or orthotopic liver transplantation (OLT: 44 pts). TAE procedures were done by injection of a mixture of cytostatic drug, lipiodol and sponge particles to hepatic artery. Histopathological evaluation was done according to tumour type, number of nodules, tumour size, rate of necrosis, existence of satellite nodules and tumoral tissue regrowth in capsular or pericapsular areas. Recurrence time and patterns with respect to various categories of tumoral characteristics were compared and cumulative disease free survival was calculated. Disease free died patients were censored. The difference between groups was determined by Log-Rank test.

Results: Complete necrosis of the tumoral mass was achieved by TAE in 20 pts (43%) of RES group and 9 pts (20%) of OLT group. Mean follow-up, beginning from the operation date for RES and OLT groups were 1.6 (0.04-6.6) and 2.6 (0.2-9.7) years respectively. Twenty-one (45%) cases of RES group (mainly hepatic) and 11 (25%) cases of OLT group (mainly extrahepatic) recurred within a mean recurrence time of 1.6 (0.2-5.5) and 1.1 (0.3-3.7) years for RES and OLT groups respectively. An overall significant difference was found between disease free survival of OLT and RES groups. Cumulative disease free survival rates for two groups with regard to remained viable liver tumoral mass after TAE are presented in the table.
The purpose of this study was to define the prognostic factors after surgical resection of bile duct carcinomas at the hepatic bifurcation. The retrospective single centre experience details 151 patients after surgical resection of central bile duct carcinoma performed between 1 January 1971 and 31 December 1995. In 151 patients resection of the tumour was accomplished by resection of the bile duct bifurcation either alone (Group I, n = 31), or in combination with hepatic resection (Group II, n = 71), or combined with hepatic and vascular resection (Group III, n = 39). Survival analysis was performed by the Kaplan-Meier method and the relationship between each of the clinicopathological variables and survival was assessed by the log rank test. The multivariate results were confirmed using Cox proportional hazard regression. The overall hospital mortality was 9.9% and depended on the extent of resection (Group I 6.1%, Group II 7.8%, Group III 17.1%). After exclusion of hospital deaths the overall patient survival according to Kaplan-Meier was 29.3% at 5 and 15.9% at 10 years with a median of 2.0±0.24 years. An univariate survival analysis identified tumour size, lymph node metastases, residual tumour stage and tumour grading as factors with a statistically significant prognostic impact. Survival prognosis was not influenced by the site of the tumour according to the classification of Bismuth and Corlette, the extent of resection, the UICC-stage, perineural and vascular invasion, age and sex. In a multivariate Cox regression analysis only lymph node metastases and residual tumour stage proved to be of independent prognostic significance. This single center report demonstrates that resection of central bile duct carcinoma is feasible in many patients and a favourable outcome after resection is mainly determined by curative resection and the absence of lymph node metastases.

Conclusion: When associated with complete tumoural necrosis, TAE before surgical treatment of HCC correlates with a more favourable disease free survival rate following surgery, compared to incomplete necrosis achieved by TAE before surgery.

76. Comparison of palliative endoscopic and surgical procedures in biliary carcinoma

M. Kraemer, R. Leppert, M. Sailer, D. Denzer, K.-H. Fachs, A. Thiede
Chirurgische Klinik der Julius-Maximilians-Universität, Jena; Schneider-Straße 2, 07798 Würzburg, Germany

Carcinoma of the extrahepatic biliary ducts and the papilla of Vater are rare but prognosis is particularly grim in cholangiocarcinoma, since the disease frequently becomes symptomatic only in advanced stages. Therefore in most cases curative surgery is no longer an option. Palliative measures aim mainly at alleviating the troublesome symptoms of obstructive jaundice, for which there are useful surgical and endoscopic procedures.

Methods: Retrospective study and follow-up of all patients with carcinoma of the extrahepatic biliary tract and the papilla of Vater, who were treated at the University Hospital Würzburg. Department of Surgery, during the years 1982-1990. Criteria examined included disease stage, histology, diagnostic and therapeutic procedures, complications, survival time.

Results: In the period covered altogether 32 patients (22 biliary carcinoma, 10 papillary carcinoma) received hospital treatment. At the time of diagnosis 72% of patients with biliary carcinoma were already at an advanced disease stage IV, compared to only 20% of patients with papillary carcinoma. Infiltration of neighboring structures or metastases at the time of diagnosis were particularly common in carcinoma originating from the upper third of the bile duct. Only 1 of 22 patients with biliary carcinoma could be operated with curative intention, compared to 6 of 10 patients with papillary carcinoma. For palliative treatment of biliary carcinoma a bileo-enteric-anastomosis (BEA) was performed in 13 cases (complications 62%, 30-days-mortality 9%, average survival time (ST) 11 months). In three further cases a drain was placed operatively (complications 100%, 30-DL 100%). Endoscopic drainage was performed in four cases (complications 50%, ST 2 months). One patient refused further treatment. BEA was performed in three of four cases with papillary carcinoma treated palliatively (complications 33%, 30-DL 33%, ST 12 months), one case was drained endoscopically (ST 10 months).

Conclusions: Despite the grim prognosis of biliary carcinoma operative exploration aiming at establishing a palliative bile-enteric anastomosis seems feasible in most cases. In cases where BEA is not possible, endoscopic or percutaneous drainage procedures can offer an alternative superior to the operative placement of drains.

77. Prognostic factors after resection of hilar cholangiocarcinoma (Klatskin-tumour)

J. Klempnauer, G. J. Ridder, R. van Waevelsiek*, M. Werner*, A. Weimann, R. Pichlmayr
Clinic for Abdominal and Transplantation Surgery, Hannover Medical School, Hannover, Germany; *Department of Pathology, Hannover Medical School, Hannover, Germany

The purpose of this study was to define the prognostic factors after surgical resection of bile duct carcinomas at the hepatic bifurcation. The retrospective single centre experience details 151 patients after surgical resection of central bile duct carcinoma performed between 1 January 1971 and 31 December 2010. Prognostic factors included disease stage, histology, surgical radicality, survival. The endpoint of treatment was defined as complete tumoral necrosis. Disease stage, histology, surgical radicality and survival were assessed by the log rank test. Survival prognosis was not influenced by the site of the tumour according to the classification of Bismuth and Corlette, the extent of resection, the UICC-stage, perineural and vascular invasion, age and sex. In a multivariate Cox regression analysis only lymph node metastases and residual tumour stage proved to be of independent prognostic significance. This single center report demonstrates that resection of central bile duct carcinoma is feasible in many patients and a favourable outcome after resection is mainly determined by curative resection and the absence of lymph node metastases.

78. Increased radicality in the surgical treatment of hilar cholangiocarcinoma

P. Neubaus, S. Jonas, N. Kling, W. O. Bechstein
Dept of Surgery, Virchow-Clinic, Humboldt-University Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany

Radical resection for hilar cholangiocarcinoma is rendered difficult by the proximity of the tumour to vital structures and a microscopic infiltration via perineural sheaths and lymphangiosis carcinomatosa. We report our concept of a gradually increasing radicality, comprising a surgical spectrum that ranges from hilar resection to the combination of total hepatectomy, partial duodenopancreatectomy, resection of the hepatoduodenal ligament and liver transplantation (LTX + Whipple's procedure). The rationale of the latter surgical approach was to use a non-touch technique to eradicate the entire biliary system. From August 1988 to June 1995, 70 patients underwent surgical resection of a hilar cholangiocarcinoma. Operative procedures included hilar resection (n = 9, 1-5-year mortality: 67%±40%), hemihepatectomy (n = 20, 1-5-year mortality: 68%±17%), extended heptemipatectomy (n = 12, 1-5-year mortality: 74%±0%), trisegmentectomy (n = 10, 1-5-year mortality: 90%±40%) and LTX + Whipple's procedure (n = 13, 1-5-year mortality: 68%±40%). Our data suggest that the actuarial 1- and 5-year survival improves with increased surgical radicality. Four patients, in whom a bile duct cancer was an incidental finding after liver transplantation, are not shown as well as 2 patients who died from liver failure after hemihepatectomy and Whipple's procedure. Portal vein resections were performed in 18 of 53 patients undergoing partial hepatic resections. One- and 5-year survival in these patients were 89% and 38%, respectively, compared to 61% and 5%, respectively, when the portal vein had not been resected.

Extended and radical surgical procedures may offer the only chance of cure to a selected subset of patients suffering from hilar cholangiocarcinoma. As a considerable peri-operative mortality after combined LTX + Whipple's procedure can still be observed, the true potential and limitations of this new therapeutic concept still need to be elucidated. However, even if the peri-operative mortality is taken into account, its long-term benefit will only be approached by trisegmentectomy and portal vein resection.

79. Peripheral hepatojenunostomy as palliative surgical treatment for non-resectable bile duct carcinoma of the liver hilum

H. J. Schiltt, A. Weimann, J. Klempnauer, B. Nashan, R. Pichlmayr
Klinik für Abdominal- und Transplantationschirurgie, Medizinische Hochschule Hannover, Germany

Hilar resection, frequently in combination with an (extended) liver resection is the surgical treatment of choice for hilar bile duct carcinomas (Klatskin tumours). Because of their location in close proximity to the vascular structures of the hepatic hilum, however, many of these tumours are already unresectable at the time of surgical exploration. While liver transplantation may offer a curative option in few patients, palliative diversion of the bile is the goal of treatment in the others. However, endoscopic stent placement through the tumour area is not always possible and occlusion or displacement are frequent complications, and PTCD requires an external drainage for the rest of the patient's life. To achieve better palliation, we have performed hepatojenunostomy by resecting the edge of the liver, thereby exposing one
or more dilated peripheral bile ducts, and then anastomosing the resection surface to a Roux-en-Y loop.

Results: (1) Between 1982 and 1995 we have performed peripheral hepatectomy in 29 patients with Klatskin tumours. (2) The hepateojejunoanastomosis was bilateral in 21 patients, only right or left in five and all three patients, respectively. (3) Surgical complications (small anastomotic leak and re-reoperation) occurred in two patients. (4) Hepateojejunoanastomosis was definitive palliative treatment in 23 cases and a bridge to transplantation or resection in six cases. (5) Mean survival after palliative surgery only was 6 months. (6) Hepateojejunoanastomosis led to a marked decrease or normalization of bilirubin in all but two patients.

Conclusions: Peripheral hepateojejunoanastomosis is a safe and effective palliative treatment for patients with irresectable central bile duct tumours of the liver hilum. In individual cases it can also serve as a bridge to transplantation and void the infectious risk of an external drainage.

81. Is local excision of pT1-ampullary carcinomas justified?

P. Klein, B. Reingruber, O. Dworak, W. Hohenberger

Department of Surgery, Friedrich-Alexander University, Erlangen-Nürnberg

Carcinomas arising within the ampulla of Vater are rare but constitute a definite pathological entity. This is reflected in better prognosis of ampullary carcinomas compared with carcinomas originating from the head of the pancreas or from the biliary tract. Local excision of tumours of the papilla was first described by Halsted in 1900. Since 1935 Whipple's procedure or other modifications of pancreaticoduodenectomy have been regarded as the surgical standard for malignant carcinomas. Local tumour excision is seen as an alternative, limited to benign lesions or elderly patients or patients in poor medical condition, unfit for extensive surgery.

Interestingly, the reports on these high risk patients with defined early stage (pT1), locally excised low grade (G1/2) carcinomas, showed substantially reduced complication rates and survival figures similar, and in some series even better than those of pancreaticoduodenectomy.

Studies of local resection of pT1 carcinomas of the ampulla of Vater are mainly episcopic and unbiased trials with sufficiently large numbers of comparable cases are still lacking because pancreaticoduodenectomy is considered the standard procedure for all radically operable carcinomas of the ampulla of Vater.

We present here our series of 35 patients with pT1 (G1-3) carcinoma of the ampulla of Vater. Whipple's procedure was performed in 26 cases and local excision of the ampulla in nine.

We propose that local excision of carcinomas of the ampulla of Vater is justifiable under the following conditions:

- When the tumour is limited to the ampulla of Vater as diagnosed by pre-operative endoluminal sonography (uT1) and UICC-staging (pT1).
- When it is graded G1 or G2 and there is no lymphatic infiltration and the tumour is completely resected (R0).

Under these conditions perioperative morbidity and mortality were significantly reduced compared with more extensive surgery. There was no local recurrence of tumour in our study and long-term survival rates were comparable with Whipple's procedure. This implies that lymphatic spread is limited to localized disease and the feasibility of the proposed procedure may therefore be analogous to localized resections in other malignant tumours, e.g. carcinoma of the rectum.

82. Resectional surgical procedures for pancreatic cancer. Results in 84 cases

S. Comunale, L. Troiano, S. Napolitano, A. Blanco, A. Giambasso, P. Iadini, C. Gitanu, A. Leutini, F. Lurci

Doctor Troiano Lorenzo, General Department of Surgery, Hospital Vit. Emanuele III-Gela (CI) Italy

Surgical resection for adenocarcinomas of the pancreas carries considerable mortality and morbidity and only rarely results in long-term survival. Although resection is the only potentially curative treatment for pancreatic cancer, typically fewer than 10% of all patients have disease sufficiently localized for surgical extirpation. Today the debate still continues on the proper selection of patients for such radical procedures. We review here our experience with pancreatic resection in the management of pancreatic malignancies.

Material and methods: Eighty-four patients underwent resection in our Department during the years 1974-1996. Fifty-five patients underwent duodenopancreatectomy, 13 total pancreatectomy. Forty-five patients underwent vascular resection (seven duodenopancreatectomy, six total pancreatectomy and one distal pancreatectomy) and eight pyloruses preserving pancreaticoduodenectomy. In the last six years 17 patients underwent subtotal extended duodenopancreatectomy as the procedure of choice. Histological examination showed 81 ductal adenocarcinomas and three adenocarcinomas. Node metastases were found in 34 patients. The tumour was well differentiated in 50 cases, moderately differentiated in 24 and poorly in 10 cases. Actuarial survival (excluding operative mortality) was carried out by the product limit method of Kaplan and Meier.

Results and conclusions: The resection was considered radical in 72 patients (85.7%) and palliative in 12. Overall hospital mortality and morbidity were 14.3% and 42.6%. In the last eight years hospital mortality decreased to 3% and resectability rate increased from 16.4% to 34.4%. Morbidity and mortality rates were 35% and 12.7% after duodenopancreatectomy, 38.4% and 7.7% after total pancreatectomy and 18.7% and 6.2% after distal pancreatectomy. Mortality and morbidity rates were 30% and 42.6% after vascular resection and the same rate was found in pylorus preserving pancreatectomy. After standard Whipple operation, morbidity and mortality rate were 40% and 14.3% versus 35% after extended subtotal duodenopancreatectomy. Five-year survival rate was 14.5% and 38.4% after duodenopancreatectomy, 0% after total pancreatectomy and 20% after distal pancreatectomy. No statistical difference was found in survival rates and standard Whipple resection. In our experience there were no differences in patients who underwent standard Whipple procedure or subtotal duodenopancreatectomy. Vascular resection improved resectability from 16% to 34.4%, and no difference in survival was seen between vascular resection and other resected patients. Survival in our patients with malignant tumours, e.g. carcinoma of the head of the pancreas, Preliminary report of an alternative operation to total pancreatectomy. Eur J Surg Oncol 1998; 14: 387-92.

83. Isolated hyperthermic liver perfusion with TNF-α and melphalan

P. Lindner1, S. B. Holmberg,2 P. Naredi1, H. Kierulf-Nielsen3, T. Schersten1, L. Hafstrøm1

Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden. 1Department of Surgery, Midtheds Hospital, Målilla, Sweden. The Interferon Research Institute, Hjörningen, Denmark and 4Department of Surgery, University Hospital of Norrland, Umeå University, Umeå, Sweden

In order to determine the toxicity and efficacy of isolated liver perfusion with TNF-α and melphalan a phase I study was performed. Ten patients with unresectable metastatic tumours in the liver (leiomysarcoma, colorectal and melanoma) were pretreated with 3 x 106 U leukocyte IFN daily two days prior to the perfusion. The liver was isolated and inflow catheters inserted in the hepatic artery and the portal vein. The hepatic veins were drained via a catheter in the retrohepatic caval vein. The venous blood flow from the lower extremities and from the splanchnic circulation was bypassed to the and portal vein. The liver circulation was perfused with unheated blood and melphalan a phase I study was performed. Ten patients with unresectable metastatic tumours in the liver (leiomysarcoma, colorectal and melanoma) were pretreated with 3 x 106 U leukocyte IFN daily two days prior to the perfusion. The liver was isolated and inflow catheters inserted in the hepatic artery and the portal vein. The hepatic veins were drained via a catheter in the retrohepatic caval vein. The venous blood flow from the lower extremities and from the splanchnic circulation was bypassed to the and portal vein. The liver circulation was perfused with unheated blood and melphalan a phase I study was performed. Ten patients with unresectable metastatic tumours in the liver (leiomysarcoma, colorectal and melanoma) were pretreated with 3 x 106 U leukocyte IFN daily two days prior to the perfusion.

Four out of ten evaluated patients had a partial remission (PR) in the liver. These remissions lasted for > 4, 5, 6 and 7 months. Four patients had stable disease (SD) and two patients who died during the early post-operative period were classified as progressive disease (PD). We conclude that perfusion with TNF-α and melphalan is a feasible treatment. Even though the morbidity is associated with a large tumour burden, the probability that TNF-α in high involvement, degree of tumour differentiation and radia
85. Sequential resection of hepatic and pulmonary metastases in patients with colorectal cancer
S. Piltz, H. Diesenmann, C. Müller, F. W. Schildberg
Department of Surgery, Klinikum Grosshadern, Ludwig-Maximilians-University Munich, Marchioninistr. 15, D-81366 Munich, Germany

During the last 16 years 12 patients with colorectal carcinoma underwent sequential resection of both hepatic and pulmonary metastases. Two patients were found to have synchronous pulmonary or hepatic metastases (Dukes D). In two further cases liver and lung metastases occurred at the same time after 11 and 44 months, respectively, following primary colorectal resection.

Patients subsequently developed liver metastases after 31.5 months (median 19; range 2-98 months) and lung metastases after 47 months (median 36; range 5-142 months). Only in one case pulmonary metastases preceded liver metastases.

Median survival from diagnosis of primary colorectal tumour was 64 months (range 23-183), from liver resection 23 (range 8-85), and lung resection 19 months (range 6-43).

Compared to patients with only hepatic (median survival: 38 months) or pulmonary metastases (median survival: 30 months) survival time was not significantly different (P=0.18).

Conclusions: In selected cases, patients with synchronous or metachronous hepatic and pulmonary metastases of colorectal carcinoma should be considered for resection as it offers the only possibility for long-term survival.

86. Patterns of recurrence in melanoma patients after sentinel node biopsy
J. Borgstein, H. J. Pijpers, A. H. van Hattum
Department of Surgery, Department of Nuclear Medicine and Department of Pathology, Free University Hospital, Amsterdam, The Netherlands

Previous studies have demonstrated the efficacy of sentinel node biopsy (SN). Using a different lymph node mapping techniques false-negative rates of up to 4% have been reported. However, the long-term risk of failures after SN biopsy and the effects of distant recurrence and survival are unclear. The results of a single institution study are reported.

Methods: Since August 1993 all patients with clinical stage I cutaneous melanoma were treated according to our SN-protocol. Following primary excisional biopsy, (dynamic) lymphoscintigraphy using Tc-99-labelled nanocolloids is performed localizing the drainage basin and number of SNs. At operation intracutaneous blue-dye is combined with a handheld gamma probe to efficiently and completely remove the SN. Patients with a positive SN undergo regional completion lymph node dissection (LND) of the mapped basin. All patients are prospectively followed.

Results: In all 143 patients (144 melanomas) one or more SNs were identified and removed. Sixteen patients had double basins. In 30 SNs (28 patients) micrometastases were detected on routine immunohistological examination and LND followed. In 23 (72%) of these specimens the SN was the only involved lymph node. One hundred and fifteen patients had a negative SN and, after a median follow-up of 15 months; there have been no regional recurrences in previously mapped basins. Seven patients of all 143 have had recurrences: four patients in-transit and three patients distant metastasis.

Conclusion: (1) These data re-affirm the accuracy of the SN concept and the described technique appears extremely reliable (0% false negative); (2) A system of pathological staging of positive lymph nodes may reduce the number of negative completion LND; (3) The patterns of recurrence seem to be influenced by the SN procedure in stage I melanoma patients and will undoubtedly affect long-term survival.

87. The gamma-probe guided sentinel lymphadenectomy—a new standard in the treatment of malignant melanomas
D. Bachtler, B.-R. Bailea, H. Vogt, H. Bächle
1Dept of Dermatology and Allergology; 2Dept of Nuclear Medicine; 3Dept of II. Surgery, Augsburg, Germany

Background: This strategy is based on the fact that malignant melanomas are drained by one and then serially to several individual lymph nodes within the nearest lymph node station.

Aim of the study: By the histopathological examination of the removed sentinel lymph node (SLN) we have the possibility to select a group of patients clinically according to a stage I or II (AJCC/UICC) but already have to attach micromorphologically to a stage III and who are profiting of a lymph node dissection of the corresponding region.

Method: We practise a gamma-probe guided sentinel lymphadenectomy (SLNE) in patients with melanomas from a Breslow tumour thickness of 1 mm upwards after injecting a colloidal 99m-Tc labelled tin (II)—sulfur colloid solution around the tumour respectively the scar if the melanoma has been previously excised previously.

Results: By gamma-probe guidance the detection and exclusion of the SLN succeeded in all cases. We performed 34 SLNEs in 49 patients (24 male, 25 female) aged from 37 to 74 years. In eight cases we found micrometastases, and subsequent material of the radical lymph node dissections contained no further metastases.

Conclusions: The SLNE is a reliable technique with minimal complications that enable us to select a group of patients who will benefit from a radical lymph node dissection.

88. Immunolymphoscintigraphy and sentinel node biopsy in high-risk stage I melanoma patients
Gen. Surg. 1, Nucl. Med. Unit, European Institute of Oncology; via Ripamonti 435, Milan 20141, Italy

Sentinel node biopsy (s.n.b.) is now a well accepted way of managing patients presenting with high risk primary melanoma. (i) the sentinel node (s.n.) in a lymph node station is not always close to the skin incision, necessitating a larger operative field. (ii) the lymphatic drainage can sometimes skip the first nodal station and, as a result, the s.n. will be located in different lymph node regions. Percutaneous lymphoscintigraphy using Tc-99m-labelled colloid has been shown to resolve both these problems but cannot help to define the presence of microscopic metastases. Eleven patients have been identified. Nine patients were clinical stage I and, except the initial two patients of the series, all received both s.n.b. and percutaneous lymphoscintigraphy, while two patients were stage II and received percutaneous lymphoscintigraphy only. An anti-melanoma labeled monoclonal antibody (185 Tc Fab') MoAbs 255.285, Sorin Biomedica) instead of a non-specific radionuclide like colloids, an equal amount of radionuclide also in the contralateral side as a control. Dynamic images were acquired for the first 5 minutes after injection, followed by static views at 10, 15, 30 minutes and 1, 3, 24 hours post injection. In all but one stage I patients studied with percutaneous
lymphoscintigraphy the s.n. was easily visualized at least 60 minutes after injection of the radiotracer. The intra-operative mapping technique consists of injecting 1 ml or more of vital dye in the skin adjacent to the primary tumour, nodular melanoma (42%) was found more frequently than superficial spreading melanoma (44%). Eighty-six percent of primary tumours were classified as advanced stages (pT3a, b and pT4, UICC 1987).

One hundred and seventy-four patients (174/437 = 40%) were surgically treated, and in 70 cases resection of the tumour mass (R0, UICC 1987) could be achieved (70/174 = 40%). Total removal was possible particularly in non-visceral metastases, but never in cases of multiple organ involvement. A median survival of 13 months after curative resection was observed. After non-radical procedures (R1, R2, UICC 1987), the prognosis was significantly worse and did not differ statistically from that without surgical therapy: 6 months vs 3 months median survival time. In single patients, survival times over several years were observed.

Surgical therapy of distant metastases in melanoma should be based on a strict patient selection and is only advantageous for those patients whose tumour can be removed completely. Surgical procedures other than complete resection should be restricted to symptomatic or complicated disease. According to the present status, radiotherapy, chemotherapy or immunotherapy neither as single nor as combined treatment modalities offer an statistically significant improvement in survival, in spite of several reports of complete remissions.

89. Loco-regional melanoma recurrence in a previously dissected lymph node basin: contribution of iterative surgery

G. Houvenaeghel, P. Baque, J. J. Gréb, J. Hardwisen, J. R. Delpeyro, J. J. Bonerandi
Institut Paoli-Calmettes, 232 Bd Sainte Marguerite, Marseille Cedex 9, France

The aim of this study is to examine the efficacy of a subsequent dissection in patients with loco-regional melanoma recurrence. Between 1984 and 1994, 118 therapeutic lymph node dissection (LND) for 79 patients with nodal metastasis were performed. Patients were 47 men and 22 women with a mean age of 53 years old. The site of the primary melanoma were extremity in 41 cases (52%) (upper: 14, lower: 27), trunk in 29 cases (34%), head-neck in 7 cases (9%), and in 2 cases an unknown primary lesion. Lymph node dissection were as follows: axilla in 66 cases (55%), inguinal in 29 cases (28%), ilio-inguinal in 19 cases (16%), lombo-aoric in 2 cases in two cases and cervical in two cases. In 28 cases (35%) a second therapeutic lymph node dissection was performed: 24 of them (86%) developed recurrence in the same nodal basin in which a lymphadenectomy had been performed or in continuity with the first LND and no evidence of distant metastases and in four cases recurrence site were different.

Mean time recurrence were in these 28 cases: 35.6 months after initial treatment (Ext: 10-123) and 12 months after the first LND (Ext: 3-41). The number of nodes removed at the initial dissection ranged from 6 to 38 and 3 to 24, with a mean of 13 and 10 respectively for 51 patients with one LND only and for the 28 patients with a second LND. The number of nodes involved at the initial dissection were respectively for the same group ranged from 1 to 31 and 1 to 16, with a mean of 5 and 1. Among these 28 patients, a third therapeutic LND was performed for loco-regional recurrence in nine cases (32%), in the same nodal basin in which a lymphadenectomy had been performed in eight cases and in different site in one case. Mean time recurrence after second LND was 18 months (Ext: 1-56).

A fourth LND had been necessary in two cases for axillary recurrence within these two cases an unknown primary lesion. An enlarged resection was performed 21 times (21/119: 17.4%): in six cases for first LND (7.7%), in 10 cases for second LND (36%) and in five cases for the third LND (5%).

Two and five actuarial survival years were respectively 86 and 49% for the 79 patients. Eighty-six and 47% for the 51 patients submitted to one LND, 89 and 47% for the 28 patients submitted to a second LND.

Conclusion: Approached in this fashion, only a subgroup of patients will show recurrence in a previously dissected nodal basin, a few of whom can be salvaged by a second dissection, with interesting results in term of survival and local control. However, enlarged resection is frequently required.

90. Surgical treatment of metastatic melanoma at distant sites

J. Gilh, Th. Meyer, Ch. Haas, W. Hohenberger
Dept of Surgery, University Hospital Erlangen-Nuremberg, FRG

Distant metastases of malignant melanoma are generally considered as incurable due to the unfavourable prognosis. At a review of the melanoma registry at the Surgical Department of the University Hospital Erlangen between 1969 and 1994 identified 437 patients with distant melanoma metastases. Most of the patients had distant lung metastases (26%), followed by distant lymph node (16%) and cutaneous (11%) metastases and also in the gastrointestinal tract (10%), the liver (8%) and the central nervous system (6%). Regarding the histology of the primary tumour, nodular melanoma (42%) was found more frequently than superficial spreading melanoma (44%). Eighty-six percent of primary tumours were classified as advanced stages (pT3a, b and pT4, UICC 1987).

One hundred and seventy-four patients (174/437 = 40%) were surgically treated, and in 70 cases resection of the tumour mass (R0, UICC 1987) could be achieved (70/174 = 40%). Total removal was possible particularly in non-visceral metastases, but never in cases of multiple organ involvement. A median survival of 13 months after curative resection was observed. After non-radical procedures (R1, R2, UICC 1987), the prognosis was significantly worse and did not differ statistically from that without surgical therapy: 6 months vs 3 months median survival time. In single patients, survival times over several years were observed.

Surgical therapy of distant metastases in melanoma should be based on a strict patient selection and is only advantageous for those patients whose tumour can be removed completely. Surgical procedures other than complete resection should be restricted to symptomatic or complicated disease. According to the present status, radiotherapy, chemotherapy or immunotherapy neither as single nor as combined treatment modalities offer an statistically significant improvement in survival, in spite of several reports of complete remissions.
Abstracts

95. The induction of increased microvascular permeability, causing the vascular leak
N. Finnegan, H. P. Redmond, M. L. Da Costa and D. J. Boucher-Hayes
Royal College of Surgeons in Ireland, Department of Surgery, Beaumont Hospital, Dublin 9, Ireland
The administration of recombinant interleukin-2 (rIL-2) is limited by the induction of increased microvascular permeability, causing the vascular leak syndrome (VLS). In this study the in vivo antineoplastic effects of the β-amino acid taurine in combination with rIL-2 were investigated and its impact on lung injury was examined. Lung metastases of B16 melanoma cells were established in mice via tail vein injection. Treatment groups included: rIL-2 (50,000 IU/0.5 ml), taurine (50 mg/0.5 ml), taurine + rIL-2 and rIL-2 + glycine. Beginning on day 10, treatments were given i.p. injections every 8 h for five days. On day 18 mice were sacrificed; lungs were removed, weighed and metastases counted, spleens were excised to obtain single cell suspensions and to establish splenocyte antimelanoma activity.

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<td>Local Tx</td>
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The response rate was:

Discussion/conclusion: ILP is a valuable therapeutic modality in the regionally advanced melanoma, with acceptable systemic and local toxicity, and significant loco-regional control of the disease, improving the quality of life of the patients.

The chemosensitization with DTIC, does not increase the toxicity. More cases are necessary to evaluate its impact in disease control.

93. Release of big-endothelin during and after isolated limb perfusion with high-dose tumour necrosis factor α
J. Haier, P. Hohenberger, P. M. Schlag
Robert-Rössle-Hospital for Oncology; Virchow-Klinikum, Humboldt-University of Berlin, Lindenberger Weg 80, 13122 Berlin, Germany
Problem: Using high-dose tumour necrosis factor α (TNFα) in isolated hyperthermic limb perfusion (ILP) high response rates were described in the treatment of malignant melanoma and soft tissue sarcoma. The administration of TNF leads to severe local and systemic side effects and the endothelin system seems to play an important role in the pathogenesis of vascular disorders (limb, renal, pulmonary) during and after ILP. The aim of our study was to investigate the release of big-endothelin (ET) as a member of the vasoactive family.

Method: Twenty-one patients with malignant melanoma or soft tissue sarcoma were treated with TNFα-ILP. Mean tissue temperature during ILP was 39.8°C. Extracorporeal circulation lasted 2.55-5.05 h. Pre-operative values of ET were determined after induction of general anaesthesia before any surgical procedure. During ILP blood samples were taken simultaneously from the perfusate and from a central vein at 15' and 75' after application of TNFs and in short intervals until 72 h after reperfusion. ET was determined by a radiolabeled immunoassay.

Results: Pre-operatively, ET values were within the normal range. During the warming period, a significant increase was found both in the perfusate ($P<0.001$) and in the systemic circulation ($P<0.05$). After application of TNFs a further significant elevation of ET concentration was observed in the perfusate ($P<0.05$). Immediately after reperfusion, an elevation of systemic serum concentration was detected for $3 h$. Values reached 5-fold the normal serum levels and returned to pre-operative concentrations within $14 h$. There was a significant correlation between tissue temperature and release of ET ($r=0.91; P<0.05$).

Conclusion: Major systemic and local side effects, mainly cardiovascular disturbances, after ILP with TNFα are mediated by cytokines and other vasoactive mediators. A rapid release of ET to the perfusate was found during ILP starting during the warm up period. It increased dramatically after the application of TNFs. The systemic release of ET after ILP could be one mechanism responsible for different side effects.

Miscellaneous

94. Is curative resection of metastasis following free dissemination possible?
C. Müller, F. Lühe, F. Speakherg, F. W. Schildberg
Department of Surgery, Klinikum Großhadern, Ludwig-Maximilians-University, Marchioninistrasse 15, 81377 München, FRG
About 60% of patients suffering from solid tumours experience dissemination of their disease, where tumour cells may spread to all organs. It is unknown, whether patients with metastasis following solitary free dissemination (fdm) and without other malignant manifestation will benefit from surgical therapy. Between January 1984 and December 1994, 54 patients with different primaries (bronchogenic (BC, n=13), breast (MC, n=6), colorectal (CoRe, n=8), kidney (HN, n=9), melanoma (MM, n=11) and rare malignancies (RM, n=7) were operated radically because of solitary fdm in thyroid (n=8), adrenal (n=15), pancreas (n=10), kidney (n=3) or soft tissue (n=60).

Depending on the location of the primary (BC, MC, CoRe, HN, MM and RM) the tumour-free interval was $6.1\pm8.8/21/61.5/59$ and 31 months with a mean survival rate after the first resection of a fdm of $19/7/6/5/634$ and 25 months.

Overall mean survival was $102\pm15$ months, after resection of the first fdm, 5-year survival was 28%. Only one patient remained tumour-free following resection of an adrenal-metastasis of a bronchogeneic carcinoma.

Conclusion: Operative treatment of solitary fdm often will lead to long survival times, complete response will be achieved only in single cases. Resectional therapy will be indicated only under palliative intention.

95. The anti-tumour efficacy of taurine and recombinant interleukin-2 in vivo
N. Finsegan, H. P. Redmond, M. L. Da Costa and D. J. Boucher-Hayes
Royal College of Surgeons in Ireland, Department of Surgery, Beaumont Hospital, Dublin 9, Ireland
The administration of recombinant interleukin-2 (rIL-2) is limited by the induction of increased microvascular permeability, causing the vascular leak syndrome (VLS). In this study the in vivo antineoplastic effects of the β-amino acid taurine in combination with rIL-2 were investigated and its impact on lung injury was examined. Lung metastases of B16 melanoma cells were established in mice via tail vein injection. Treatment groups included: rIL-2 (50,000 IU/0.5 ml), taurine (50 mg/0.5 ml), taurine + rIL-2 and rIL-2 + glycine. Beginning on day 10, treatments were given i.p. injections every 8 h for five days. On day 18 mice were sacrificed; lungs were removed, weighed and metastases counted, spleens were excised to obtain single cell suspensions and to establish splenocyte antimelanoma activity.

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<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of metastases (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>155 ± 24.0</td>
</tr>
<tr>
<td>rIL-2 (50,000 IU)</td>
<td>64 ± 21.J</td>
</tr>
<tr>
<td>rIL-2 + Taurine (10 mC)</td>
<td>21 ± 6.4*</td>
</tr>
<tr>
<td>Taurine (10 mC)</td>
<td>111 ± 32.8</td>
</tr>
<tr>
<td>rIL-2 + Glycine</td>
<td>66 ± 29.8</td>
</tr>
</tbody>
</table>

* $P<0.05$ vs Control; ** $P<0.05$ vs rIL-2; ~ $P<0.001$ vs Control.

Treatment of tumour-bearing mice with rIL-2 alone resulted in a significant reduction in tumour nodule incidence compared to a control group, while the group receiving rIL-2 + taurine showed an even further significant reduction. To examine the effect of taurine on rIL-2 induced pulmonary oedema, west and dry lung weights were assessed. Animals receiving rIL-2 showed a significant ($P<0.01$) increase in mean wet lung weight compared to control lung weight, while mean wet lung weight of the rIL-2 + taurine group was significantly less ($P<0.05$) than that of the rIL-2 group. Animals that received rIL-2 + taurine in vivo demonstrated significantly enhanced ($P<0.05$ at ET 001 and 405) splenocyte-mediated antimelanoma activity ex vivo compared to animals receiving rIL-2 alone. We conclude that taurine may have an important role in modulating both the anti-cancer efficacy and
101. Influence of conventional surgery versus laparoscopic procedures on human monocytes cytokotoxicity

Department of Surgery, Free University Hospital, Amsterdam, The Netherlands

Introduction: Impairment of immune functions is associated with increased tumour growth. Surgery leads to a post-operative immune suppression, which is assumed to be related to the severity of surgical trauma. Therefore it is hypothesized that laparoscopic surgery does not impair the immune system as measured by the cytokotoxicity of monocytes. HLA-DR expression on monocytes and interleukin-6 plasma levels.

Methods: In the present study, parameters of immunocompetence were measured in patients undergoing conventional surgery (colon resection, Nissen fundoplication and cholecystectomy) and compared to the same procedures performed by laparoscopic technique. Blood was taken 24 hours before surgery, and 24 and 96 hours after surgery. Cytotoxicity of monocytes was measured against a colorectal tumour cell line using the MTT-assay HLA-DR expression on monocytes by flow cytometry and plasma interleukin-6 levels.

Results: Cytotoxicity of monocytes was decreased 24 hours after the conventional procedures. Also a decrease in HLA-DR expression was seen, together with increased plasma IL-6 levels. In patients who underwent the same procedures laparoscopically, no decrease in cytokotoxicity was observed. HLA-DR expression was mildly depressed and IL-6 levels only slightly increased in these patients.

Conclusion: Conventional surgery leads to a post-operative immune suppression as measured by the cytokotoxicity of monocytes. HLA-DR expression and IL-6 plasma levels. After laparoscopic surgery these immune functions are unimpaired. This protective effect might be of significant importance, especially in patients undergoing surgery for cancer.

102. ‘Physiological’ doses of IL-2 reduce endotoxin sensitivity and TNF production whilst improving lymphocyte function in an animal tumour model

P. Rendshaw, S. Fielden, O. Eremia, D. B. Gough
Department of Surgery, University of Aberdeen, Medical School, Aberdeen AB9 2ZD. UK

Critical illness (cancer, trauma, burns) is associated with increased susceptibility to sepsis, a process mediated by increased levels of TNF and reduced IL-2 production due to decreased lymphocyte function. The aim of this study was to examine the effect of low ‘physiological’ doses of IL-2 on in vivo survival post-endotoxin challenge and in vitro spleen cell TNF production and lymphocyte function in an animal tumour model. Three groups of mice (n=10) were inoculated intramuscularly, two with LLC tumour (gpi A+B) and one with medium (gp C). All groups received twice daily i.p. injections on days 17-22 post-inoculation. Group A received IL-2 (1001U), groups B and C vehicle (5% dextrose). At day 22 mice were sacrificed and spleen cells isolated. TNF production was assessed using an (1001U), groups B and C vehicle (5% dextrose). At day 22 mice were sacrificed and spleen cells isolated. TNF production was assessed using an ELISA assay. Lymphocyte blastogenesis was measured in response to ConA. Matched groups were challenged with endotoxin (75 ug i.p. E. coli) and survival assessed.

Group A had improved lymphocyte function compared to groups B + C (P=0.0005*) and reduced TNF production compared to group B (P=0.0005*). This correlated with an improved survival in group A of 50% compared to group B (P=0.0001) after an in vivo endotoxin challenge. IL-2 appears to have an important immunomodulatory role with regard to lymphocyte function. TNF production and endotoxin sensitivity in cancer.

103. Tumouricidal activity of antiseptic agents. An experimental in vitro and in vivo study

G. Basha, F. Peininkx, P. Yap
Dept of Abdominal Surgery and Hepatology*, University Clinic Gasthuisberg, Leuven, Belgium

Background: Recurrent cancer may be due to implantation of exfoliated tumour cells. The intra-operative use of tumouricidal agents is not popular.

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Aim: to test and to compare the tumouricidal efficacy of some antiseptic agents on carcinoma cells.

Methods: In vitro. Integrity assessment of SW620 human carcinoma cells with the trypan blue exclusion test before and after 30 min incubation in distilled water (DW), chloramin 0.5% in DW, polivinyl pyrolidone iodine (PVPI) 0.01, 0.05, 0.1 and 5% in DW. In vivo. 5.10^5 SW620 human carcinoma cells were resuspended in 200 µL buffer solution after 30 min incubation in medium or in one of the above mentioned agents, immediately followed by sc. injection in SCID (severe combined immunodeficient) mice. Mice were sacrificed after 8 weeks. Subgroups of mice were injected a higher (adjusted) number of tumour cells in order to approximate a final concentration of 5.10³ presumably living tumour cells despite the pre-treatment with an agent.

Results:

<table>
<thead>
<tr>
<th>Agent</th>
<th>In vitro viability</th>
<th>In vivo tumour growth N of mice</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>100%</td>
<td>16/20</td>
<td></td>
</tr>
<tr>
<td>Dist. water</td>
<td>89%</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>PVPI 0.01%</td>
<td>77%</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>PVPI 0.05%</td>
<td>12%</td>
<td>0/3</td>
<td></td>
</tr>
<tr>
<td>PVPI 0.1%</td>
<td>3%</td>
<td>0/3</td>
<td></td>
</tr>
<tr>
<td>PVPI 5%</td>
<td>0%</td>
<td>0/3</td>
<td></td>
</tr>
<tr>
<td>Chloramine</td>
<td>2%</td>
<td>0/3</td>
<td>*</td>
</tr>
</tbody>
</table>

*Adjustment for N of living cells was only 40% (10³ cells injected), but mice were followed for 12 weeks.

Conclusion: Distilled water and PVPI 0.01% are not tumouricidal, not in vitro, not in vivo. In contrast, PVPI 5% and chloramine 0.5% kill all tumour cells and prevent their growth in vivo. PVPI 0.05 and 0.1% are less effective in vitro than 5%, but can prevent in vivo proliferation unless an adjustment for the residual number of living tumour cells is performed. These data indicate the importance of the magnitude of the tumour inoculum, hence the need to use a maximally effective ‘killing’ agent.

104. Suicide gene therapy; a definite immunological component to the bystander effect

I. M. Pape, S. Gagandeep, B. Green, S. Christmas, D. Klatzmann, A. R. Kinella and G. J. Poston
Department of Surgery, University of Liverpool, Liverpool, UK. * L’Hopital de la Pitié Salpetrière, Paris, France

The integration and over-expression of the herpes simplex virus type 1 thymidine kinase (HSV1-TK) gene is localized tumours, results in tumour regression following the administration of the specific nucleoside analogue ganciclovir (GCV). Although only 10-20% of the tumour cells take up the HSV1-TK the neighbouring cells die as a consequence of what has been termed the ‘bystander effect’. Subcutaneous tumours were created by injection of 1 x 10³ cells of the mouse colon adenocarcinoma cell line MC26. All control mice were co-injected with 1 x 10³ cells of the NB16 packaging cell line expressing the nis-lacZ gene and all test mice were co-injected with 1 x 10³ cells of the PLJ-TK packaging cell line expressing the HSV1-TK gene. The mice were divided into four groups: nude Balb/C mice into a control and a test group (Groups 1 and 2 respectively) and normal Balb/C mice into a control and a test group (Groups 3 and 4 respectively). Seven days were allowed for retroviral gene transduction and tumour growth prior to treatment with GCV twice daily for five days. At the end of this time the animals were sacrificed and the tumour volume in each group was assessed. A significant tumour regression was observed in the test groups versus the control groups. The mean tumour volume was 42.1 mm³ in the control groups (Groups 1 and 3) compared with 3.3 mm³ in the test group 4 (P<0.01). The test group for nude mice did not spend with the same efficacy only reaching a reduced tumour volume of 20.5 mm³ (P<0.05). These data demonstrate a near complete regression of established subcutaneous tumour in normal Balb/C mice following the successful transduction of the HSV1-TK suicide gene followed by treatment with GCV. The same was not true for the Balb/ C mice suggesting a strong cell mediated immune component to the ‘bystander effect’. Suicide gene therapy may trigger a more general anti-neoplastic action by facilitating a specific anti-tumour immune response.
We have also developed an animal model for the treatment of multiple hepatic metastases in the rat, with the packaging cell line delivered by hepatic artery cannulation. In this way it may be possible to treat patients with otherwise inoperable hepatic metastases by suicide gene therapy.

105. Generation of tumour specific cytotoxic T lymphocytes using bone marrow generated dendritic cells in a murine model of breast carcinoma

E. C. Coveney, B. Clary, A. Porgador, E. Gilboa, H. K. Lyerly
Department of Surgery, Duke University Medical Center, Durham, NC, USA

Dendritic cells (DC) are potent antigen presenting cells and are regarded as crucial for the priming of an immune response. Our aim was to test whether bone marrow generated DC are capable of inducing tumour specific cytotoxic T lymphocytes (CTL) against a murine breast carcinoma (4T1). DC were grown from Balb/C mice by culturing lymphocyte-immunodepleted bone marrow in murine GM-CSF containing media for 10 days. Balb/C mice (3/group) were immunized intradermally with 1 x 10^6 DC mixed with 2 x 10^7 lethally irradiated 4T1 cells on day 0. Mice in control groups were given intradermal inoculations of 1 x 10^6 DC or lethally irradiated 4T1 cells alone. Booster intraperitoneal immunizations of 2 x 10^7 lethally irradiated 4T1 cells were given on days 7 and 14. Splenocytes were removed from mice 10 days after immunization and cultured in vitro with lethally irradiated 4T1 cells for 5 days. Functional activity of CTL was tested in standard micrototoxicity assays. 4T1 target cells were incubated with ^51CrO4 for 2 hours, washed, resuspended and combined with effector cells for Effector:Target (E:T) ratios of 100:1, 50:1 and 25:1 and cells incubated for 4 hours. Harvested samples were counted in a gamma counter. Results for CTL cytolysis are shown below as mean percent specific lysis for experiments done in triplicate. Significantly greater lysis of 4T1 at all E:T ratios was seen using DC and 4T1 induced CTL (ANOVA, P=0.014). There was effective cold target inhibition of DC and 4T1 induced CTL using autologous 4T1 cells but minimal non-specific competition with the NK/LAC cell target VAC cell (data not shown). Similar results were obtained using 4T1 cell lysate to prime DC for immunization.

These results provide a rationale for the use of bone marrow generated DC in cytotoxic T lymphocyte mediated immunotherapy of breast cancer.

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127. Long-term tissue effects in the normal and surgically manipulated canine liver following intra-operative radiotherapy (IORT)

Departments of Surgical Oncology, Radiotherapy, Pathology, and Radiobiology, University Hospital Groningen, The Netherlands

Introduction: After liver resection for colorectal metastases microscopic residual disease is often left behind. With external beam irradiation (EBRT) a tumouricidal dose cannot be applied without damaging normal tissue. Theoretically IORT offers the ability to treat not curatively resected liver metastases. Introducing IORT clinically in the treatment of liver metastases, dose guidelines concerning the tolerance of liver tissue to single high dose irradiation have to be provided. The long-term histopathological tissue changes of normal and surgically manipulated canine liver following different IORT-doses were experimentally investigated.

Materials and methods: Twenty-five caged underwent a partial liver resection of the right median lobe, the resection surface as well as the non-surgically manipulated left median lobe of the liver were intra-operatively irradiated. The dogs were divided into five groups of dogs, each group received a different dose of 0.10, 20, 25, or 30 Gy IORT. Three months, 1, 2, and 5 years following the IORT procedure one dog out of every dose group was electively sacrificed for histopathological purposes.

Results: There were no surgical or IORT related complications during a follow-up of 5 years. Liver enzymes were slightly elevated post-operatively, returning to normal values within 6 months. Elective sacrifice performed 3 months following IORT showed uncomplicatedly healed resection planes. Microscopically at 3 months capsular thickening was seen, at 1 year severe fibrosis of the irradiated area presented which had grossly resolved at 3 years following IORT leaving a defect at the site of irradiation. At 5 years, possibly due to regeneration, this defect had almost disappeared. Microscopically histopathological alterations were seen: capsular thickening, subcapsular fibrosis, bridging portal fibrosis and liver cell atrophy were especially prominent in the higher dose groups, minimal after 3 months but more severe after 1 year follow-up. At 3 and 5 years these histopathological alterations had almost completely disappeared. Vascular alterations were surprisingly less distinct.

Conclusion: Five years following IORT, doses up to 30 Gy to normal and surgically manipulated canine liver are well tolerated without any morbidity. If IORT is limited to small volumes of liver tissue liver function will not be affected and safe application in this model is warranted.

Gynaecology

96. Analysis of 129 pelvic exenterations for gynaecological malignancies

G. Houvenaeghel, V. Moutardier, F. Bladou, J. Hardwigsen, M. Martino, J. R. Delpepo
Institut Paoli-Calmettes, 232 Bd Sainte Marguerite, Marseille Cedex 9, France

One hundred and twenty-nine patients underwent pelvic exenteration between January 1980 and December 1995 in the Department of Surgery of the Institut Paoli-Calmettes. Ninety-two exenterations were done for carcinoma of the cervix (71%), Ninety-two exenterations were done for carcinoma of the cervix (71%). Thirty-seven were done for other malignancies: endometrium: 13, ovarian: 16, and other: 6. The exenterations were performed alone in 31 cases and in association with a radiotherapy in 18 cases. Therapeutic options are dependent of relapse site, medio-pelvic, latero or pan-pelvic, and on previous treatments. We present our experience with the first 24 months after treatment, with an exclusive pelvic site in 50 to 85% of cases. Thirty-two patients were operated on surgical treatment of pelvic cervical cancer relapse. For the curative group (n = 69), 68%, 60% and 44% at 2, 3 and 5 years.

97. Surgical approaches for recurrent pelvic cervical cancer

G. Houvenaeghel, M. Martino, F. Bladou, M. Resbeut, J. R. Delpepo
Institut Paoli-Calmettes, 232 Bd Sainte Marguerite, 13273 Marseille Cedex 9, France

Cervical cancer relapse occurred in six to 50% of cases, essentially during the first 24 months after treatment, with an exclusive pelvic site in 50 to 85% of cases. Therapeutic options are dependent of relapse site, pelvic, extra pelvic, and on previous treatments. We present our experience on surgical treatment of pelvic cervical cancer relapse.

Material and methods: From July 1980 to February 1994, 74 patients with cervical cancer relapse were proposed for surgical resection and 49 patients have had a surgical procedure for pelvic cervical cancer relapse (median relapse occurrence: 10.5 months). Forty-four tumour relapses (90%) were localized in the pelvis (vaginal recurrence five, midpelvic 19, ileorectal 10, urethral 4, and parapelvic 3). In 5 cases, pelvic tumour relapse was associated with distant metastases. The median tumour size was 40 mm. Surgery was performed alone in 31 cases and in association with a radiotherapy in 18 cases.
98. Prevention of radiation enteritis and pelvic floor reconstruction by a polyglycolic acid 910 (Vicryl®) mesh in gynaecologic malignancies

J. F. Rodier, J. C. Jander, D. Rodier
Department of Surgical Oncology, Paul Strauss Cancer Center, 3 Rue de la Porte de l'Hôpital, F-80783 Strasbourg Cedex, France

The synthetic absorbable polyglycolic acid 910 mesh (Vicryl, Ethnor S.A., Neuilly sur Seine, France) is composed of a copolymer of glycolide and lactide acids. Inert, non-pyrogenic, non-antigenic, and non-teratogenic, this material has been shown to produce minimal tissue reaction after total resorption by hydrolysis. Complete resorption occurs on post-operative day 60-90.

For prevention of radiation enteritis, the 'intestinal mesh sling' elevated the small bowel above the pelvic external beam radiation field. The average age of the 36 patients was 53 years (range 33-70). The surgical procedures were performed in 86.1%, especially for uterine carcinomas (88%). Pre-operative treatments were administered in 20 cases (55%). These were no per-operotive deaths. The average (cumulative) dose ranged from 4500 to 5000 cGy.

Conclusion: These results are comparable with other surgical series in the literature. Most authors limit the surgical indication for mediopelvic cancer relapses and mostly for vaginal relapse. We recognize a treatment for other pelvic tumour relapses in selected patients because a pelvic reconstructive technique in these cases allowing an increase in both survival and quality of life.

99. Endometrial carcinoma (EC) in women with breast cancer (BC): clinical characteristics and prognosis. (On behalf of the French Federation of Comprehensive Cancer Centers)*


*Centre L. Berard, Lyon, 1 Centre A. Vauquelin, Nancy, 2 Centre P. Struass, Strasbourg, 3 Centre R. Huguenin, Saint Cloud, 4 Institut Bergonié, Bordeaux, 5 Centre A. Lyaussagne, 6 Centre P. Lamarque, Mompellier, 7 Centre O. Lamberet, Lille, 8 Institut G. Roussy, Villejuif, 9 Centre CR, Regard, Toulouse, 10 Centre GE, Leclerc, Dijon, 11 Centre H. Beccquerel, Rouen, 12 Centre P. Pupin, Angers, 13 Centre E. Marnius, Rennes, 14 Federation Nationale des Centres de Lutte contre le Cancer, France

Methods: A multicentre, hospital-based, case-control study, was organized in 14 French cancer centers, comprising 143 women in whom an EC had been diagnosed between 1976 and 1990, at least 6 months after BC. A total of 519 women with BC were individually matched on date of birth and date of diagnosis of BC. Data have been particularly studied according to clinical features and prognosis of EC.

Results: In a multivariate analysis, previously reported (**), the risk of EC was significantly increased with use of Tamoxifen (TAM) (mOR=4.4, P<0.0014), length of treatment more than 3 years (mOR=3.9, P=0.016) and pelvic radiotherapy (mOR=3.2, P=0.02). Among the 143 EC, 45 women did not receive TAM and 98 patients were treated. For 54 of them, EC diagnosis have been done during therapy and after treatment ended for 44 others. No significant difference (SD) for age at onset of EC between the three subgroups was reported. Women with EC occurring after completion of TAM were younger at time of BC diagnosis than those observed on untreated women or with EC during TAM (median age: 50 vs 61 and 61 y: P<0.01). The median cumulative dose of TAM was not significantly different between the two exposed groups nor the median duration of exposure. Tumours in FIGO 2+ stage were more frequent among treated women (P<0.01) and among women with EC after treatment ended (33.2% vs 15.4%). Most of the EC were differentiated adenocarcinoma (no SD) but six mixed Mullerian tumours were reported in the exposed group. The proportion of ovarian irradiation was significantly greater in the subgroups of EC occurring after treatment (P<0.05), without association between pelvic irradiation and histological types. Median follow-up after EC was respectively 40 m and 84 m for treated and untreated women. The overall survival (OS) after EC was shorter for the TAM treated group than for untreated women (P=0.005) and survival was better for EC observed during TAM therapy than for those diagnosed after end of treatment (P=0.02).

Hypothesis: EC observed during TAM therapy occurred in older women, less often treated with pelvic irradiation, and had a better overall survival. A neoplasia could have been present before TAM therapy. Women with an EC observed after treatment ended were younger, more often treated with ovarian irradiation and had a poorer prognosis. Hypothetical oncogenic effect of TAM and/or pelvic radiotherapy will be discussed.

**9th congress of the Senologic International Society (SIS), Houston, 1996.**

100. Inhibition of tumour growth by spilling blood in the peritoneal cavity

Department of General Surgery, University Hospital Rotterdam-Dijkzigt, The Netherlands

Despite potentially curative surgical resection of gastrointestinal cancers (GI), the creation of a temporary pelvic diaphragm was a safe and effective procedure (reduction of morbidity 14.3% vs 34.4%), especially in patients with unsuitable omentum and in those women in whom myocutaneous flaps were not performed.

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98. Prevention of radiation enteritis and pelvic floor reconstruction by a polyglycolic acid 910 (Vicryl®) mesh in gynaecologic malignancies

99. Endometrial carcinoma (EC) in women with breast cancer (BC): clinical characteristics and prognosis. (On behalf of the French Federation of Comprehensive Cancer Centers)*

100. Inhibition of tumour growth by spilling blood in the peritoneal cavity

Supported by these encouraging results, prevention of radiation enteritis could be recommended in gynaecologic malignancies, mainly after radical curative surgery and with a palliative intent. Following ultra radical surgery, the creation of a temporary pelvic diaphragm was a safe and effective procedure (reduction of morbidity 14.3% vs 34.4%), especially in patients with unsuitable omentum and in those women in whom myocutaneous flaps were not performed.

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106. The incidence of primary malignant bone tumours in Ireland
P. G. Murphy, M. Sharp, P. Dervan, M. Cavanagh, B. Hurson
Cappagh Orthopaedic Hospital, Finglas, Dublin 11, Ireland
Primary malignant bone tumours are rare, being less than 0.5% of all neoplasms in man, and account for less than 1% of all deaths from malignant disease. Accurate estimates of their incidence are difficult to collect and this is reflected in the literature by approximate values being quoted. Difficulties with accuracy and completeness include population cross border migration and availability of multiple centres within a country. Ireland being an island offers the clinician an ideal opportunity to accurately report the incidence of these malignancies. Our population is 3.5 million and has a limited number of referral centres treating these patients. We reviewed all primary malignant bone tumours treated between 1990 and 1995. There were 102 patients in this six year period, a significant number of whom had metastatic disease on presentation. The table shows a summary of the five tumour types:

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Age</th>
<th>Incidence/million/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma</td>
<td>54</td>
<td>22.33 ± 13.87</td>
<td>2.55</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>21</td>
<td>50.63 ± 19.05</td>
<td>0.99</td>
</tr>
<tr>
<td>Ewing's sarcoma</td>
<td>18</td>
<td>17.15 ± 7.12</td>
<td>0.84</td>
</tr>
<tr>
<td>Parosteal osteosarcoma</td>
<td>5</td>
<td>22.51 ± 8.65</td>
<td>0.24</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>4</td>
<td>47.87 ± 12.50</td>
<td>0.19</td>
</tr>
</tbody>
</table>

There were 64 males and 38 females, the incidence per 100,000 per year being 1.61 and 0.36 respectively. To our knowledge this study represents the only reported incidence for primary malignant bone tumours for a single country.

107. Active tibial and femoral titanium growing prostheses in limb sparing salvage for children's bone sarcomas (10 years experience)
N. Delopino, G. Delopino, S. Alkallaf, L. Benkedra, B. Markowska, V. Subovici, J. C. Desbois, R. Debre
48 Bd Serrurier, 75019 Paris, France
New techniques in the care of children with malignant bone sarcomas have contributed to the increased length of survival. Quality of life now becomes a priority and has led to improved techniques of limb-sparing reconstructive surgery.

Growing children, especially those younger than 10 years of age have until recently fared better with amputation than with limb saving reconstruction because of the unavoidable limb length discrepancy. After Simeone, then Lewis, we tried to use an expandable and adjustable prosthesis. We review here our 10 years experience with tibial and femoral prosthesis and our successive models, the last growing without open surgery.

Methods: Prostheses are produced in titanium, chosen for its better mechanical properties, twice as elastic and light as stainless steel. The prosthesis is manufactured following the recommendations of the surgeon for each patient with individualized size. The prosthesis is done with three elements: one special growing part, one epiphyseal part, one tibial or femoral stem. The size of the epiphyseal part is small enough to be inserted from a semi-quantitative scoring system. Differences between groups were analysed using the Student's t-test.

Results: In experiment 1 the mean score in the experimental group with regard to tumour growth on all scored intra-abdominal locations was significantly less as compared to the control group (P<0.005).

Conclusion: Surprisingly, the presence of blood in the intra-abdominal cavity did not enhance the formation of tumour colonies, but, to the contrary, had an inhibitory effect on intra-abdominal tumour growth. Our data suggest, that erythrocyte-related factors are responsible for this phenomenon.
between 10 and 70, 33 were male and 28 were female. In 53 cases the metastasis was detected after a follow-up X-ray. In 48 cases, the lesions were unilateral, 10 of these being multiple. In 13 cases, the lesions were bilateral. The time lapse between the treatment of primary tumour and the detection of metastasis was less than or equal to two years in 36 cases, with 16 synchronous metastases. In 25 cases, it was over two years.

The necessary operating conditions were: stable tumour, absence of extrathoracic metastasis, possibility for complete resection of lesions, respiratory compatible with the size of the pulmonary resection.

Conclusion: The surgical treatment of pulmonary metastases is beneficial when it is well indicated. It frequently prolongs survival (five years survival rate in 25% of cases). In some cases, it cures completely, and is there always an improvement in the quality of life. The best results are obtained when the free interval is over two years and when the resection of metastases is complete. There is no difference between limited resections (segmentectomy, wedge resection) and extended resections (lobectomy, pneumonectomy) which is why the first are preferred to avoid larger resection.

The resection of pulmonary metastases is usually carried out by thoracotomy, but it is possible to use sternotomy for bilateral lesions as long as a complete resection is possible. Post-operative chemotherapy has not as yet been proved effective. On the other hand, re-operating for recurrences gives good results: five years survival rate in 58% of cases. Currently for peripheric localizations, we sometimes use thoracoscopy.

The question today is: what is the role of pre-operative chemotherapy? It enables us to test the sensitivity of metastases, occasionally to decrease their volume and to destroy micrometastases. Pre-operative chemotherapy is probably useful to clarify the surgical indications.

110. Multimodal interactive simulation of soft tissue sarcoma surgery

C. Vecchio**, R. Palmuto******, P. L. Santì****, F. Badolato***
* Division of Surgical Oncology, National Institute for Cancer Research,
Genova, Italy. ** Department of Plastic and Reconstructive Surgery, IST,
University of Genova, Italy; *** Department of Communication, Compute,
and System Sciences, University of Genova, Italy. **** Institute of Radiology,
University of Genova, Italy. ***** Department of Medical Oncology. National
Institute for Cancer Research, Genova, Italy.

Resection of a soft tissue sarcoma requires that the tumour be located so that an acceptably wide margin of normal tissue can be obtained between the edge of the tumour and the adjacent critical, non-resectable structures, such as major nerves, vessels, bone, and important tendons. To date, because of the inability to obtain a clear margin at those sites and still retain acceptable function, approximately half of patients with extremity sarcomas are subjected to amputation. We consider that for these malignant tumours it is possible to perform conservative surgery within a multidisciplinary approach to define the extent of the tumour and the connections with the surrounding tissues and anatomic structures. Total 3D reconstruction of the tumour size, shape, and relations with surrounding structures using CT, MRI, sonography, and angiography images can make simulated radical resection of tumour, thus sparing normal tissues. With our approach, starting from three 2D MR images (of 256 × 256 pixels) at the same slice location in a given patient, a new single image representation of all three parameters is generated by using the false-colour technique on a HP9000/735 workstation in a standard UNIX and X-11 environment. A transformation linking together the MR parameters and the RGB (red, green, blue) colour components is used. In particular, PD corresponds to green, T1 to blue, and T2 to red, respectively. The image is the composite result of the mapping of the three parameters by means of false colour. It is displayed using a resolution of 24 bits per pixel via a HP CRX24 graphics board. It is also possible to apply the same type of processing in a 3D-VR environment. In this case we are dealing with three stacks of images which together make up a multiparameter volumetric dataset. The three parameters for each voxel specify the RGB colour components of the voxel to a volume rendering program. The colour statistics of the image can be used to interactively segment out different tissues for removal and/or closer inspection. In this interactive environment, we can dynamically render and update a stereo display using field sequential presentation of left and right eye views on the monitor, with Cristal Eyes LCD shutter eyewear (StereoGraphics Inc., San Rafael, CA, USA) to view it. An ARINC standard computer system based on low-frequency magnetic fields (Polhemus Fastrak) has been chosen. All this, in our experience, has greatly facilitated the simulation of soft tissue sarcoma excisions.

111. Retrospective study of retroperitoneal sarcomas: analysis of prognostic factors

Clínica Oncológica 1-6º Piso. Instituto Português de Oncologia. Porto, R/Dr. Antonio Bernardino de Almeida, 4200 Porto, Portugal.

Introduction: Retroperitoneal sarcomas are rare tumours, representing between 0.1 and 0.2% of all cancers, and 10 to 20% of the soft tissue sarcomas. In this retrospective study we have evaluated the natural history, the therapeutic management and analysed the prognostic factors of these tumours.

Material and methods: We have studied 43 patients with retroperitoneal sarcomas admitted to our Institution between April 1974 and December 1994. The clinical presentation, type of surgical treatment, patterns of recurrence and adjuvant therapies were analysed. The overall survival was analysed according to the following factors: age, sex, size, histological type and tumour grade. Representative tumour sections were reviewed by the same pathologist, with special attention to histological type and grade. The survival curves were determined using the Kaplan-Meier method, and the statistical analysis applied were the log-rank and chi-square tests.

Results: The most frequent histological types were the liposarcoma and the malignant fibrous histiocytoma. A complete resection of the primary tumour was accomplished in 64% of the patients, being one the most statistically significant prognostic factor (P = 0.002). The rate of complete resection was only influenced by the histological grade (P < 0.003). Involved adjacent organs were resected in 50% of the cases. In those patients submitted to a complete resection of the primary tumour, 81% developed tumour recurrence during a median follow-up time of 24 months. Of these 86% were local recurrences.

The overall survival at 5 years was 30%, being 42% for patients with low grade tumours and 65% for those with high grade. The histological type, age, sex and size of the tumour did not significantly affect the prognosis.

Conclusion: Retroperitoneal sarcomas are associated with high rate of local recurrence. The histological grade and the complete resection of the primary tumour were the most important prognostic factors. Our study reinforces the concept that a complete surgical resection of the tumour and adjacent organs when involved must be the goal of the surgical treatment of these tumours.

113. The angiogenic growth factors bFGF, TGF-81, TGF-82 and VEGF in systemic and tumour venous blood of soft tissue sarcoma patients

P. M. Vogt, M. Lehnhardt, D. Wagner, H. U. Steinau
Universitätsklinik für Plastische Chirurgie, Handchirurgie und
Schwerbrandverletzte, BG-Klinik Bergmannsheil, Bärbel-de-la-Camp Platz 1,
44789 Bocum, Germany

Soft tissue sarcomas of the extremities contribute to only 0.9% of all neoplasms. Even in experienced hands radical surgical resection is followed by a recurrence rate of 7 to 35%. The reasons for this high percentage are not yet clear. Since angiogenesis is a key factor in tumour growth we have investigated concentrations of the angiogenic peptide growth factors bFGF, TGF-81, TGF-82 and VEGF in systemic and soft tissue sarcoma venous blood of 50 consecutive patients undergoing radical tumour resection: liposarcomas, malignant fibrous histiocytomas, fibrosarcomas, clear cell sarcomas, leiomyosarcomas and others. Systemic venous blood was obtained preoperatively, during surgery, 1 hour, 1 day and 1 week after operation. Ten cc of venous blood was collected from tumour veins during surgery. Samples were centrifuged and stored at −70 °C. Levels of cytokines were measured with a monoclonal sandwich ELISA (R&D Systems© USA). All samples were analysed in duplicates on a Dynatech® ELISA plate reader. Pre-operative (6.2 ± 5.9 pg/ml, P < 0.03) and intra-operative (4.9 ± 2.9 pg/ml, P < 0.05) values of bFGF (mean±SD) were significantly elevated compared to values 1 hour (3.4 ± 2.1 pg/ml), 1 day (3.9 ± 1.4 pg/ml) and 1 week (4.1 ± 2 pg/ml) after operation and although to bFGF values obtained in normal subjects (2.7 ± 1.2 pg/ml). Concentrations of bFGF determined in tumour blood were significantly higher than serum levels (234 ± 256 pg/ml, P < 0.05), but significant lower than controls obtained from large soft tissue wounds (e.g. musculocutaneous flap donor sites, 473 ± 273 pg/ml). Further the values of VEGF and TGF-81 showed no significant difference and update a stereo display using field sequential presentation of left and right eye views on the monitor, with Cristal Eyes LCD shutter eyewear (StereoGraphics Inc., San Rafael, CA, USA) to view it. An ARINC standard computer system based on low-frequency magnetic fields (Polhemus Fastrak) has been chosen. All this, in our experience, has greatly facilitated the simulation of soft tissue sarcoma excisions.
114. Treatment of infections with massive prostheses after limb salvage (29 cases)


* Hop. R. Debré-48 Bd Serrurier, 75019 Paris, France, ** Hop. H. Mondor, 93900 Creteil, France

With the dramatic improvement of conservative surgery in patients with bone sarcoma (often immunosuppressed), infection becomes one of the most serious complication. The aim of this monocentric study is to precise the frequency, the etiologic factors and the therapeutic approach of this bad situation.

Patients: From 1983 to 1995, we have operated more than 450 patients with bone sarcoma, out of them 246 benefited from construction with massive prostheses often combined with massive allograft. Follow-up was 6 months minimal. Age of patients was 4.5 to 82 years (mean 24 years). The histology was osteosarcoma (141), Ewing's sarcoma (39), chondrosarcoma (38), fibrous sarcoma (23), giant cell tumours in others. All patients were operated by the surgeon of the team. In 184 cases, patients received chemotherapy, and radiotherapy in 43 cases. The mean follow-up is 5 years. Twenty-six deep infections led to one or more surgical procedures.

We have seen also three patients for recurrence of deep infection initially treated elsewhere. Altogether, we have treated 29 deep infections.

Methods: Three patients were amputated as emergencies because of septicaemia resulting from profound marrow depression. Twenty-six patients were initially operated to clean the prosthesis. Antibiotics were adapted to the germ isolated during the surgical procedure. When this method was ineffective, one second cleaning with removal of the prosthesis was performed with replacing the new prosthesis in the same time.

When infection remained after these procedures, removal of the prosthesis was performed with interposition of a spacer with cement loaded with antibiotics. The new prosthesis was placed in a second time, when cutaneous and muscular problems were resolved.

Results: At the last control, out of 29 patients, 13 were amputated, initially, 10 secondarily, following a mean of six ineffective procedures. Sixteen patients benefited from conservative surgery but the new prosthesis could be placed in 13, following a mean of four surgical procedures, and with a result inferior to this obtained with the initial prosthesis.

Analysis by case, and statistical analysis show the bad prognostic import of initial radiotherapy, of distal locations, and of insufficient muscular coverage.

Conclusion: Infection of massive prostheses is the most serious orthopaedic complication. It leads to amputation in nearly 40% cases. Treatment must be preventive: obtaining a good coverage of the prosthesis using large musculo-cutaneous flaps, avoiding any radiotherapy, shortening the length and the extent of alapiosis (role of GCSF?), using prostheses able to limit reinterventions.

When infections appear, the therapeutic approach depends on other treatments (chemotherapy etc.) and the history of the patient. Factors for success are early removal of the prosthesis, effective antibiotic therapy, improvement of the muscular coverage, and use of prostheses without cement.

115. Axillary and chest wall paediatric rhabdomyosarcoma—UKCCSG multicentre review

A. S. Adam, M. T. P. Corbally, M. G. Mott
Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland

Effective management of axillary and chest wall rhabdomyosarcoma (RMS) in children demands local and metastatic disease control, with good preservation of function. Axillary dissection is challenging, the complex neurovascular anatomy making resection with adequate margins difficult. The collective experience of these rare tumours is poorly documented in the literature.

We performed a retrospective analysis of 29 children presenting with a confirmed RMS of the chest wall and axilla between 1978–1992 (median age 4.83 years, range 3 months–13 years). There were 23 chest wall tumours, two of which were bone, one thoracic inlet and three axillary (one lateral, one anterior and one posterior). The median tumour diameter was 8 cm (1–12 cm).

The median duration of follow-up was 84 months (22–120 months).

Survivors were 27 patients (93%). Twenty-five patients received chemotherapy (86%) and 13 (45%) received radiotherapy. Of the patients 12 (41%) have survived for more than 5 years with no evidence of the disease.

The overall morbidity was low. One child with thoracic inlet RMS developed Horner syndrome and chylothorax. Subsequently ligation of the thoracic duct was performed. One child developed an incisional hernia (a latissimus dorsi flap was used for reconstruction after two ribs were resected along with the tumour). He also developed a wound dehiscence following the transection of the nerve to the serratus anterior. Traumatic ulceration was performed in one child who needed prolonged ventilation. Chest wall asymmetry was noted in a 2 year old baby after excision of the tumour and three involved ribs.

116. Tumour surgery of the pelvic bones

P. Rahoby, M. Szenszlot, I. Benszaky, S. Dubecz
Dept of Surgery, National Institute of Oncology, Budapest, Dept of Orthopaedics, SOTE, Budapest

During the past 10 years the authors operated on 27 tumours of the pelvic region, 12 of them involving the pelvic blade, six the periacetabular region, further nine the os pubis and iliacus, respectively. Most of the cases (16) were chondrosarcomas. The mean age of the patients—13 male and 14 female—was 41 years. Wide radical surgery was carried out in 11 cases, a marginal resection in 10, and intralesional resection was carried out in six patients. After a mean follow-up period of 3 years (0.5–11 years) 19 patients are alive, tumour-free, two with tumour, four died and two were lost to follow-up. Delayed wound-healing and inguinal hernia occurred in five cases, and venous thrombosis with secondary compartment syndrome and renal insufficiency developed in one on the other side.

117. Management of sacral chordoma

M. P. Nowacki, K. Herman, J. Olejdzki, A. Stelmach, P. Liszka-Dalecki
Cancer Center, M. Sklodowska-Curie Institute, ul.Findera 101, 02-781 Warszawa, Poland

The aim of this study was the assessment of possibilities of treatment for patients with sacral bone chordoma. Twenty-four patients treated in the Cancer Center were analysed. The treatment of choice was surgery combined with adjuvant radiotherapy (microscopic surgery was possible in five cases and the survivals have reached to 7 years). Radiotherapy following non-radical surgery was used in three cases in which the median survival was 5 months. Treatment using only radiotherapy provided good palliation in 13 patients in whom the median survival was 26 months. The authors suggest that in all cases of pain in the sacrum or ischium, with symptoms not resolving within 1 month, radiological investigation (X-ray or CT of sacral bone) should be carried out to exclude the possibility of malignancy. Radical treatment without causing severe disability is seldom possible. Neoplasms of sacral bone of large size, exceeding 8–10 cm should be operated by abdomino-sacral access, whereas the smaller tumours can be successfully operated by sacral access alone. In unresectable cases, radiotherapy is the best palliative measure and in patients after non-radical surgery allows for long-term survival.

118. Sternectomy and repair for primary and secondary tumours

C. Lequaglie, M. Incarbone, M. Nava*, U. Pastorino, G. Ravasi
Thoracic and * Reconstructive Surgery, National Cancer Institute of Milan, Italy

Reconstructive procedures following resection of primary and secondary malignant chest wall tumours continue to develop. From January 1980 to December 1993, 56 patients underwent surgical resection for tumours involving the sternum—22 were males, 34 females aged 16 to 75 and 23 to 77, respectively (median 48 and 53). There were 26 primary malignant tumours, 19 local or distant recurrences of breast cancer, seven miscellaneous tumours and four cases of radionecroses. Concurrent en bloc resection of the anterior ribs was performed in 41 patients, and of clavicula in 11. Resection was extended to lung in 12 patients, to pericardium in eight, to both in two, to diaphragm and pericardium in two. Reconstruction was obtained with various methods: prosthetic material associated to muscular or myocutaneous flap was used in 27 patients (48%), prosthetic material alone in 10 cases (18%), muscular or myocutaneous flap in five cases (9%). Different techniques were used in remaining patients. Pectoral major muscle was used in 16 cases, latissimus dorsi in 11, and rectus abdominis in five. The resection was considered macroscopically radical in 51 patients (91%), and there was a purely palliative intent in the remaining five cases. There was no operative mortality, and significant morbidity was limited to six cases (11%). The 3 years percentage of survival was 58% (median follow-up of 39 months), while the 5-year survival was 46% (median follow-up of 50 months). Among patients who underwent radical surgery 27 (53%) are alive and 24 (47%) are free of disease. In 24 cases of primary chest wall tumours the 5-year survival was 66%.

In our experience the resection of sternum for primary or secondary tumours followed by reconstruction with prosthetic material and/or myocutaneous flap seems to be a safe and effective treatment, which may
Abstracts

120. Advanced soft-tissue sarcoma of the extremities: results of surgery combined with intra-operative radiotherapy (IORT) and post-operative external boost radiotherapy (EBRT)

M. Schwarzbach, F. Willeke, M. Eble, U. Hinz, Th. Lehner, V. Ewerbeck, M. Wannenmacher and Ch. Herfarth

Introduction: Advanced soft-tissue sarcomas (STS) of the extremities are characterized by a high rate of local recurrences. Combined multimodality treatment made limb sparing surgery possible. While external beam radiotherapy (EBRT) is well established, there are few data available on additional intra-operative radiotherapy (IORT) applied after resection. In order to evaluate the effects of IORT we performed an analysis of our patients.

Patients and methods: Between 1991 and 1995 a total of 42 patients with advanced STS of the extremities (UICC stage IIb-IVB) received IORT. Median age of the patients was 54 years. Histology was dominated by liposarcoma (40%) and MFH (40%). Eighty percent of STS were located in the lower extremity. Wide and radical excision was used in order to achieve a macroscopic tumour in 34 patients, histology showed tumour free resection margins in 26 and positive margins in eight of these cases. In order to obtain local tumour control eight patients with either locally unresectable tumours or incurable distant metastasis were treated under palliative intention. Post-operatively EBRT was applied to a defined area including the IORT field in most of the cases (n = 33).

Results: Four wound infections, a venous vascular graft thrombosis and a cerebral infarction contributed to a peri-operative morbidity of 16%. Late complications were found in 12% of all cases (one necropathy, one muscle contracture, two fractures, and one osteitis). Mortality was 2%, caused by a lethal pulmonary embolism in an obese patient with deep venous thrombosis. Within a mean follow-up of 25 months two local failures (6%) were seen in patients treated with curative intention. The 3-year survival rate was 70% in patients treated under curative intention. However, patients who had macroscopic residual tumour left either after incomplete resection or with metastasis had a poor prognosis. These results suggest that IORT in combination with EBRT after resection is an additive treatment modality of first choice in advanced soft tissue sarcoma of the extremities: nevertheless complete surgical removal is a pre-requisite to achieve good long-term results.

121. Germ cell tumour metastases to the lung—role of surgery in multimodality therapy

A. Helvá, I. Bosányá, I. Bodrogi, L. Tőth

Department of Surgery, National Institute of Oncology, Budapest, Hungary

A total of 61 lung metastasectomies were performed for metastasising testicular germ cell tumours in the Department of Surgery of the National Institute of Oncology, Budapest, between 1980 and 1995. All but one were non-seminomatosi primaries. The intention of treatment was diagnostic and therapeutic.

The treatment of choice at stage III testicular cancer is combined chemotherapy, after the eradication of the primary tumour. Pulmonary metastasectomy is justified in cases of poor response to chemotherapy or when the pulmonary deposits seem stable. Intervention is not recommended for patients with seminomas who have continuously elevated serum marker-values. Chemotherapy should be completed before surgery and about four weeks later thoracotomy is carried out. Median sternotomy is now chosen for all patients. All palpable nodules are removed in parenchyma-saving fashion. Residual tumour is not confirmed in about 50% of removed nodules.

There is no advantage of a repeated metastasectomy in these patients. Disease free interval, response to chemotherapy, the number of deposits and histology are prognostic factors. The best results of pulmonary metastasectomy is achieved in this group of patients.

122. The results of re-operation for lung cancer

A. Cheula, M. Lucchi, A. Musi, G. Fontanini*, A. Ribeichini and C. A. Angeletti

Service of Thoracic Surgery, Department of Surgery, Institute of Pathology*, University of Pisa Via Roma 87 Pisa 56100, Italy

In the last few years the number of patients who develop a new lung neoplasm after resection for lung cancer is increasing. A new lung neoplasm may be a second primary lung cancer (SPLC), a pulmonary metastasis of the initial tumour (PM) or a local recurrence (R) (in situ and adjacent to the initial resection) of the primary cancer. During a 16-year period (1980-1995), in 54 cases of primary lung cancer with R (n = 8), PM (n = 11) or SPLC (n = 35) a re-resection was performed. Twelve patients were symptomatic, while the remaining patients had lesions detected at follow-up chest X-ray. The first operation consisted of 10 wedge resections or segmentectomies, 42 lobectomies and two pneumonectomies. The second resection was a wedge resection in 22 patients, a lobectomy in nine patients and completion pneumonectomy in 13 patients. Median interval between the two resections was 36 months (range 6-154) for the SPLC, 16 (6-108) months for the PM and 14 (6-46) for R. There were two (3.7%) peri-operative deaths. As regards post-operative staging there were five stage I and three stage IIIA in the R group in spite of 21 stage I, two stage II and 12 stage IIIA in the SPLC one. All the PM were small lesions without lymph nodal involvement. Actuarial 5-year survival after the second pulmonary resection for SPLC was 25.7% with 17 patients still alive. The 5-year survival rate in the PM group was 11.9% with two patients alive at 12 and 22 months from the second operation. Actuarial overall 5-year survival rate for patients with R was 42.8% with four patients still alive. Comparing the survival rates by means of the log-rank method we verified no significative statistical difference even a negative trend for the PM. We emphasize the role of a careful follow-up at 6-monthly intervals for the early detection of second pulmonary lesions. Whenever SPLC, R or PM occur, re-operation is the treatment of choice.
for reconstructive purposes (steel wire: 20; Vycril®: 23; Marlex®: 52) were used in 93 cases. Wounds were closed primarily (n = 43), by transpositioning of the greater omentum (n = 45), with a myocutaneous flap (n = 9) or by transpositioning of the contralateral breast (n = 7). In addition to this split-skin grafting was done in 42 cases. Averagely patients were intubated for 1 day and stayed in the intensive care unit and hospital for 4 days and 20 days respectively. Complications of the wound occurred in 36 cases. In 11 of those the transpositioned omentum got infected. Nine cases of wound necrosis occurred, seven of which were partial necrosis of the omental flap. Pulmonary complications were met after 24 resections: 10 cases of pneumonia and four embolisms occurred; three patients suffered A.R.D.S. Changes in pulmonary function were found to depend on the extent of the resection. Overall both FEV1 and vital capacity declined, their ratio remaining equal. Surgical intervention because of complications was needed in 23 cases. Among those were removal of implants (n = 9), excision of necrotic graft parts (n = 7), re-thoracotomy (n = 3) and tracheotomy for intubation (n = 2). Two patients died post-operatively after 9 and 12 days respectively.

Conclusion: From the evaluation of 103 chest wall resections and subsequent reconstruction we conclude that if performed by experienced surgeons radical surgery is a safe treatment for tumours of the chest wall. Extensive resections can be performed with limited risk of serious complications even in elderly patients. We further believe that omental flaps offer a reliable option for reconstruction, with good cosmetic and functional result and low morbidity.

124. Pulmonary metastasectomy

G. Botter, B. Pasquotti, R. Sigon
Surgical Oncology Dept, Centro di Riferimento Oncologico C.R.O., Aviano, Italy

Most soft tissue sarcoma patients and sometimes carcinoma patients, relapsing to distant sites, have only isolated or multiple lung metastases. Patients with extremity sarcomas are more likely to have distant metastatic disease, while those with retroperitoneal and visceral sarcomas tend to have local recurrence. However, the actual incidence of pulmonary metastases in patients with soft tissue sarcoma of the limbs or trunk is not known. In soft tissue sarcoma metastases, surgery may provide a disease free long-term survival (3 years) in 20-49% of patients; for isolated metastases of colorectal origin, 5 years survival rate of 9% to 57% have been reported. We agree with many authors that surgery is the standard treatment for isolated lung metastases.

Materials and methods: Between September 1987 and March 1996, 59 consecutive patients with lung metastases were evaluated for surgery in our Center. All the records were evaluated for age, management of the primary neoplasm, tumour free interval, extent of pulmonary operation, adjuvant chemotherapy and long-term survival. There were 37 men and 22 women; median age was 52 years (range 17 to 77). The primary histologic types were: sarcoma (27 patients), carcinoma (23), testicular neoplasms (4), melanoma (2), gynaecological neoplasms (3), extragonadal carcinoma (2). The sites of the original neoplastic tumour were: lungs and breast, kidney, bowels, ovary and uterus, testis, others. The median interval between primary therapy and the diagnosis of metachronous pulmonary metastases (DFI) was 12 months (range 0-112). Pulmonary metastases did not cause symptoms in 80% of the patients and were detected during standard radiographic follow-up studies. Unilateral thoracotomy was performed in 64 patients, bilateral thoracotomy in two, median sternotomy in 15 and VATS in two. We merely performed a wedge resections in 46 patients, a combined wedge resection(s) and lobectomy in six, a lobectomies in six, a pneumonectomy in one and two VATS. Seven patients have been operated twice, five patients three times and two patients four times. Forty-four patients received adjuvant chemotherapy. All the patients have been follow-up with a chest X-ray every 3 months, and thoracic CT scan every 12 months for the first 2 years and then chest X-ray every 6 months for 3 years. The overall median survival is 44 months (range 9-197). Therefore, to date, 37 patients are living, 26 of which without evidence of disease.

Results and discussion: In our experience, significant prognostic variables (multivariate analysis of prognostic factors) are: (1) complete resectability, (2) tumour type. We agree with other authors that pulmonary metastasectomy can be performed only when: (1) it is possible to remove all the metastases, (2) the tumour can be controlled, (3) the patient has sufficient pulmonary reserve to tolerate the resection(s). Median sternotomy is the surgical treatment of choice for pulmonary metastasectomies from sarcomas because the high incidence of bilateral disease. The patient, with completely surgically resected lung metastases, is disease free, but the risk to relapse is high. Thus, the necessity, after surgery, to perform an adjuvant treatment (chemo and/or radiotherapy).

125. Atrial fibrillation: pharmacologic treatment and evaluation in lung cancer surgery after thoracotomy

C. Fiorentini*, D. Cardinali*, A. Martinosti*, G. Lamantia*, M. Civelletti*, C. M. Cipolla*, M. Messetti**
* Cardiology Division, European Institute of Oncology (EIO), IRCCS, Milan, Italy. ** Thoracic Surgery Division, EIO, IRCCS, Milan, Italy

Atrial fibrillation (AF) is the most common post-operative arrhythmic complication in thoracic surgery. Not yet defined are AF incidence and clinical relevance in patients undergoing thoracotomy for lung cancer surgery and whether antiarrhythmic prophylactic medical treatment is indicated.

We evaluated 110 patients (80 males, 30 females, mean age 58 ± 9) who underwent between June 1994 and January 1996 lobectomy (52 cases), pneumonectomy (21), pleural decortication (13), atypical lung resection (17) or explorative thoracotomy (5) for lung cancer. Observation period was 11 ± 4 days post-operatively.

Results: AF occurred in 15 patients (13.6%) and in 60% of the cases by day 1; all episodes were clinically well tolerated (HR 128 ± 29, mean BP 87 ± 12 mmHg with no signs of heart failure) if promptly treated: 100% reversion to stable sinus rhythm was observed within 24 hours with intravenous amiodarone (12 patients) or propaphenon (three patients). Administration and without second drug and/ or major invasive procedures (internal/external DC shock cardioversion) being required; no correlations were observed between AF occurrence and several clinical general and cardiological specific pre-operative parameters.

Conclusion: In patients undergoing thoracotomy for lung cancer surgery AF (1) occurs in almost 14% of the cases with high prevalence (60%) by day 1; (2) is not predictable by standard clinical, cardiological, respiratory and haematologic pre-operative controls; (3) is clinically well tolerated. (4) if promptly recognized and treated in all cases revert to regular sinus rhythm. Prophylactic antiarrhythmic medical treatment is therefore not recommended.

126. Tumour cell detection in intra-operative pleural lavage in lung cancer

J. Bahr1, K. H. Berghäuser2, S. Gonzalez3, C. Kelm4, T. Zimmerman4, W. M. Hedberg5
1 Dept. of Gen. and Thoracic Surgery and 2 Institute of Pathology, Justus Liebig University, Giessen, Germany

According to the TNM classification, a malignant pleural effusion equals a T4 spread of lung cancer. The criterion is the cytologic demonstration of tumour cells.

We present the results of a prospective study in which pleural lavage was done with 300 ml physiological saline solution after opening the chest to discover whether tumour cell dissemination into the pleural cavity occurred in the early stages of lung cancer (= lavage I). A second lavage after resection of lung cancer (=lavage II) showed whether surgical manipulation of the lung parenchyma led to a tumour cell contamination of the pleural cavity.

Three hundred and ninety-one patients (306 patients with the first manifestation of lung cancer and 85 patients with non-neoplastic lung disease) underwent pleural lavage. Tumour cells were found in lavage I in 85 patients (27.8%), in 78 of them also in lavage II. Among the previously classified as stage I (pT1 N0, pT2 N0) lung cancer positive tumour cell detection was in 38.3% possible. All controls were negative, i.e., there were no false positive findings. The cumulative 5-year survival rate of curative resected non-small cell lung cancer in stage I (n = 78) was 22.1% if lavage was positive (n = 30), and 64.3% if lavage was negative (n = 48) (P < 0.05).

Therefore, detection of tumour cells in pleural lavage before resection proves that tumour cells have spread into the pleural cavity. The positive result in pleural lavage seems to be a prognostic predictor for patients with lung cancer. An adjuvant therapy should be performed for those patients with a positive intra-operative pleural lavage in lung cancer.
129. Ultrasound-guided localisation of impalpable breast lesions

Departments of Surgery and Radiology*, Derriford Hospital, Plymouth PL6 6DH

Impalpable lesions detected by mammography require accurate localisation before excision biopsy. This prospective study assesses the efficacy of ultrasound-guided localisation in terms of successful localisation of lesions and their adequate excision.

Between March 1989 and February 1996, 148 patients with impalpable lesions easily visible on ultrasound underwent ultrasound-guided localisation. Localisation was performed using an Aloka SSD 620 with a 7.5 MHz linear array probe. The depth of the lesion below the skin and its diameter was recorded. The mean age of the patients was 58.7 years (range 27.4-80.4).

The mean maximum diameter of lesion localised at ultrasound was 11.2 mm (range 3-30), compared to mean histological size of 12.6 mm (range 4-33). The mean maximum diameter of tissue removed was 57.5 mm (range 10-110), 65 specimens were weighed. The mean weight of all specimens was 37g (range 2-101), 99 of the 148 ultrasound-localised biopsies (67%) were malignant.

Excision was complete in 87 (88%) of the 99 malignant cases. Five patients had further excisions and seven proceeded to mastectomy.

Well-defined impalpable lesions have been successfully localised using ultrasound. The procedure is simple, convenient and non-invasive.

130. Prediction of responsiveness of women with breast cancer to primary tamoxifen therapy using polymerase chain reaction on fine needle aspirates

M. J. S. Lee, T. W. J. Leonard, C. N. Robson
Department of Surgery, The Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4HH

Introduction: The hormone responsiveness of breast cancer has been widely exploited in therapy. Several genes show altered expression in response to estrogen withdrawal. We have undertaken a project to develop a highly sensitive assay to measure gene expression in tumour samples from breast fine needle aspirates (FNAs) as a method to obtain prognostic information for patients receiving primary tamoxifen and to anticipate disease progression.

Methods: First strand cDNA was synthesised from mRNA purified from FNAs taken from patients with evidence of breast cancer. Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) was performed using highly specific oligonucleotides for the Estrogen Receptor (ER), Progesterone Receptor (PR), p52, Epidermal Growth Factor Receptor (EGFR), c-erbB2 and Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNAs. The PCR was modified to include 32P-dATP to allow quantification of mRNA expression by a Phosphorimag. Internal controls were included in each PCR reaction. Results were expressed relative to the expression of the house-keeping gene GAPDH.

Results: Fifteen patients undergoing tamoxifen therapy were studied. p52 expression was detected in 13 patients. ER and c-erbB2 mRNA expression was only detected in 4/15 and 2/15 patients, respectively. Seven patients expressed detectable levels of PR and EGFR. Within the range of detection, greater than 100 fold differences were noted for p52 mRNA expression between patients.

Discussion: A highly sensitive assay has been developed to examine gene expression using RNA derived from breast FNAs. Patients undergoing tamoxifen therapy showed dramatic differences in mRNA levels for the genes under investigation. This study is being extended to investigate the expression of the described genes during the course of tamoxifen treatment.

131. Assessment of morbidity from axillary dissection for breast cancer (BC): a comparative study of axillary clearance (AC) versus fat and lymph nodes suction (FLNS)

S. Ardigo, H. Mignotte, C. Batie, V. Peyrigonne, A. Bremond
Centre Leon Berard, Dept of surgery, 28 rue Laroche, 69373 Lyon Cedes 08, France

Methods: 83 women were treated for an operable BC with mastectomy or lumpectomy and axillary lymph node dissection. 38 axillary clearances were performed with a classical surgical procedure and 45 others with a FLNS. Morbidity was assessed by a questionnaire asking all the patients to record pain, weakness, numbness or stiffness (objective and subjective criteria).

Results: No significant difference was noted for number of removed nodes whatever the surgical procedure (mean: 11 nodes in each group). Duration of hospitalization was the same in this series, but unrelated to the axillary clearance procedure.

Median follow-up were respectively 9.1 months for the AC group and 7.1m for FLNS group. No difference between the two groups was noted according to arm mobility (13% in each group) nor for swelling (20% for AC group and 25% for FLNS group). Two cases of periarthritic, after radiotherapy were noted in both subgroups.

The frequency of residual pain of the treated upper limb was slightly higher for FLND group but the difference was not significant. A significant trend was noted for paresthesia, more frequent after open surgery than after axillary suction (28% vs 11%, P=0.05), and the same difference was found for residual hypoesthesia (50% vs 26%). Nevertheless, the frequency of weakness of the treated arm was lower in the AC group than in the FLNS group (28% vs 48%).

Conclusion: Benificial effect of axillary suction seems confined to sensory sequelae but a residual pain of the treated arm is frequently encountered with this surgical procedure. These preliminary results may encourage careful evaluation of this new technique. Further assessment is necessary before proposing routinely this surgical procedure to breast cancer patients.

132. The method of wound plasty after extended mastectomy

I. V. Galaychuk, R. D. Kostiushyn
Department of Oncology, Ternopil Medical Institute, Ternopil, Ukraine

Between 1992 and 1994, 9 female patients (aged 50-71 years) were treated for locally advanced breast cancer TNM. Clinically there were registered the tumours of 18 x 20 x 15 cm in size with the areas of ulceration, bleeding, chest wall infiltration. All patients underwent the Halsed operation with the partial resection of ribs (3), scapular (2) and peristreum (4). The histopathologic type of tumours were adenocarcinoma in 5 cases, angiosarcoma 3 and fibrosarcoma 1.

Postmastectomy skin and soft tissues defect was directly related to the extent of operation. The wound was closed by transferring a dorsocellobdominal cellulocutaneous flap (CCF). This flat is cut with the help of two additional incisions. One begins from the upper edge of the wound in the axilla and in arched way extends on the back to the spine. The second extends from infraerial angle of the wound down to the umbilicus. The mobilization of the CCF is done in this way to save the perforating vessels. As a result of dorsocellobdominal flap is formed, which is transferred and fixed to upper edges of the wound. Vacuum drainage is used and a pressure bandage applied.

Results: In 6 patients such plasty was successful. In 3 patients there was marginal necrosis of the transferred flap. In these cases skin grafting was performed after the necrotic tissue had been removed. Post-operative complications: arm lymphostasis 7, shoulder joint contracture 8 patients. All patients were treated by radiotherapy and/or chemotherapy in the post-operative period. No local relapses have been observed for two years.

133. ‘Arimidex’ (anastrozole): an overview of the efficacy and tolerability of ‘arimidex’ compared with megestrol acetate in postmenopausal women with advanced breast cancer

Arimidex International Study Group and Zeneca Pharmaceuticals, *CRC Dept Medical Oncology, Christie Hospital, Manchester, UK

‘Arimidex’ (Anastrozole [A]) is a new effective and highly selective non-steroidal aromatase inhibitor with a pharmacokinetic profile allowing once-daily oral administration. In two randomised trials carried out in Europe and the US, A was compared with megestrol acetate (MA) in postmenopausal advanced breast cancer patients who had previously been treated with tamoxifen for early breast cancer or advanced disease. Between March 1993 and June 1994, patients were randomised to A 1 mg (263 pts), A 10 mg (248 pts) or MA 4 x 40 mg daily (253 pts). The 3 groups were comparable with regard to their baseline characteristics. After a median follow up of 6.1 months, intention to treat analyses were done on time to progression and...
survival using the Cox proportional hazards model and on response rate using logistic regression. The results of the two trials were almost identical and the data sets were combined to give the results shown in the table below.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A 1mg</th>
<th>A 10mg</th>
<th>MA 160mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of pts</td>
<td>263</td>
<td>248</td>
<td>253</td>
</tr>
<tr>
<td>Median age (yrs)</td>
<td>65</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Median TTP (days)</td>
<td>141</td>
<td>153</td>
<td>139</td>
</tr>
<tr>
<td>Response rate*</td>
<td>35.4%</td>
<td>31.5%</td>
<td>34.0%</td>
</tr>
</tbody>
</table>

There were no statistically significant differences between either A 1mg or A 10mg compared with MA for any efficacy endpoints. Significantly more patients in the A 1mg group had a higher intensity of oedema and dyspnoea in this group compared with A. Withdrawal rate due to adverse events was 3% for both doses of A and 4% for MA. The comparable efficacy of A 1mg and 10mg is consistent with the equal potency of these 2 doses in terms of aromatase inhibition and oestrogen suppression. It is concluded that Arimidex is an effective, well tolerated treatment for advanced breast cancer in postmenopausal women.

Abstracts

134. Results after surgical treatment in locally advanced breast cancer
C. Mariotti, E. Lenti, M. Guerrieri, A. M. Pagani, E. Lezoche
Chirurgia Generale 1, Universita di Ancona, Ancona, Italy
Forty-one cases of locally advanced breast cancer, without clinically detectable metastases (stages IIIa and IIb) (UICC, 1987; AJCC, 1988), divided in 2 subgroups, have been enrolled. Group a) locally advanced breast cancer (LABC) (IIIa and IIb except T4d), group b) inflammatory breast cancer (IBC) (T4d). The present work evaluates the long-term results of the surgical treatment of locally advanced breast cancer, associated with other therapies, over a 20 year period (1975 to 1995). Disease-free survival, possible relationship between the duration of the survival and a specific therapeutic approach or the histopathological findings and overall survival have been investigated. 41 patients have been studied (equal to 3.5% of all breast cancer treated from '75 to '95): 24 LABC and 17 IBC; mean age was 53.7 years (range 30-84), 50.6 for LABC (range 30-69) and 57.7 for IBC (range 30-84). 17 women were pre-menopausal (13 LABC and 4 IBC) and 24 post-menopausal (11 LABC and 13 IBC). All patients have undergone a radical mastectomy (Halsted 24 cases; Patey 5; Madden 12). 4 cases belonging to the LABC group and 12 cases of the IBC group received postoperative therapy (CT-RT). The postoperative therapy (CT-RT-H) has been carried out in almost all cases (23 out of 24 LABC and 16 out of 17 IBC). The hormonal receptors and other risk factors status was defined in 16 cases. The 5 year survival rate for the LABC group is 51.27% and the disease-free survival is 47.34%. All patients were N+; in the subgroup with 3 or less positive lymph nodes the survival rate is 55.6%, while in the subgroup with more than 3 positive nodes the survival is 55.6%. The comparison of the survivals of the 2 groups is statistically significant (P<0.05). The 5 year survival rate of the IBC patients is 31.66%, all referring to the group of patients with 3 or less metastatic lymph nodes. None of the observed cases with more than 3 lymph nodes demonstrated a survival greater than 5 years. The comparison of the survivals is statistically significant also in this group (P<0.05). Six local recurrences (14.63%) have been observed, 5 in LABC and 1 in IBC groups. These data suggest that surgical treatment can be effective in the control of the disease. Nevertheless the involvement of more than 3 lymph nodes seems to represent the most relevant predictive prognostic factor not influenced by the pre or post operative therapy.

135. A prospective randomized trial of short versus long hospital stay after surgery for breast cancer
Th Wiggers, J. Bomnena, A van Wesch, J. E. A. Pruy, A. N. van Geel
Department of Surgical Oncology, University Hospital Rotterdam/Daniel den Hoed Cancer Center, Rotterdam, The Netherlands
The effects of reduced hospital stay after breast cancer surgery on the quality of care, incidence of surgical complications, well-being of patients and total costs of treatment were studied in a prospective randomized trial. All patients had complete axillary dissection and segmental or total mastectomy. The 'short stay' group (n=62) received early discharge with drains in place, while the 'long stay' group (n=63) remained in the hospital until the drains were removed. Mean length of stay was 4.1 and 9.0 days respectively. Research data were collected from 3 questionnaires and daily and weekly diaries. Results showed that the 'short stay' group was more satisfied with the length of stay. There were no medical or psychosocial disadvantages of early discharge and it offered a greater opportunity for social support within the family. The integral costs including the costs of home care were significantly lower for the 'short stay' treatment ($3444 vs. $4848, P=0.0001). It is concluded that early discharge after surgery for breast cancer is a cheap and safe alternative for post-operative hospital care with higher patient satisfaction and better psychosocial outcome.

Keywords: axillary dissection, hospital stay, costs

136. Chest wall resection in locally recurrent breast cancer: indications and outcome in 44 patients
I. F. Faneyte, E. J. Th. Rutgers, F. A. N. Zoetmulder and A. te Velde
Department of Surgery, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands
Introduction: Chest wall resections for breast cancer following mastectomy often are the first sign of metastatic disease. Nevertheless when faced with such recurrences regarding local control is of importance, because of the enormous morbidity caused by locally uncontrollable processes. Preferable treatment in this situation is still subject to discussion. Chest wall resection as one of the therapeutic options, is generally as feasible under very limited circumstances, because of the supposedly high morbidity caused by the operation, in patients with poor prognosis. This report aims to analyse indications and morbidity of chest wall resections in relation to survival in patients with local recurrences of breast cancer.

Materials and methods: Between 1979 and 1995 44 females underwent chest wall resection as treatment for locally recurrent breast cancer in the Netherlands Cancer Institute. Their medical records were analysed retrospectively. Pre-operative situation parameters scored were: age and nodal stage at primary diagnosis, initial treatment and subsequent disease free interval, number of relapses, presence of distant metastases and age at resection. Analysis was made of disease free and overall survival after resection and of the influence thereupon of presumed prognostic factors. The median follow-up period was 3.2 years. In all operations the surgical standards were as follows: margins of 2cm microscopically uninvolved tissue were resected around the tumour, usually the visceral pleura was the deep margin, unless en bloc resection of lung tissue or part of the diaphragm was indicated. By definition all resections included bony parts of the chest wall. Reconstructive implants for stability were used in 41 patients (steel wire 9; Vicryl 12; Marlex 20). Soft tissue reconstruction was either by primary closure (n=10) or with use of the following techniques: pedicled 1 flap of the greater omentum (n=31), transpositioning of the contralateral breast (n=3), myocutaneous latissimus dorsi flap (n=2). In 28 cases soft tissue reconstruction was completed with a split-skin graft.

Results: The mean age at diagnosis of breast cancer was 47.5 years. The median interval between first treatment and tumour progression was 3.9 years. 27% of patients had already developed distant metastases. All patients had been treated surgically at some stage prior to chest wall resection, 39 with irradiation, 10 with chemotherapy and 4 with hormones. Ages at the time of resection ranged from 31 to 79. Post-operative complications were met in 25% of cases, e.g.: 7 infections of the wound, 8 patients with lung problems (embolus, pneumonia), 1 tracheotomy for reination and 1 debridement after pleuritis empyema. Adjuvant therapy was given to 12 patients (hormonal: 8; RT: 2; both: 2). 30 patients were considered to be free of tumour after the operation (curative intent). Their median disease free interval was 3.3 years, the 5-year disease free survival rate was 35.0%. Of these patients 18 had a relapse: 1 local recurrence, 12 distant metastases and 5 had both. The median overall survival was 8.9 years; the 5-year survival rate 61.5%. The other 14 patients underwent resection with palliative intent because they already had distant metastases or because complete resection was impossible (resectional margins not free of tumour). Their median survival was 2.3 years and the 5-year survival rate was 21%. A long interval between primary treatment and recurrence correlated with a longer disease free survival after chest wall resection.

Conclusion: With chest wall resection local control can be obtained with low morbidity in patients suffering a recurrence of breast cancer. 5-year survival in patients without known distant metastases can be as high as 60%. Nevertheless this conclusion is based on the limited number of patients for which chest wall resection can be widened. For chest wall resection should always be considered as a therapeutic option for patients with locally recurrent breast cancer.
137. Sentinel node procedure in breast cancer using Tc99m-colloidal albumin

G. J. Collet1, R. Pilipes2, O. S. Hoekstra3, R. Boom1, S. Meijer1
1Department of Surgery, 2Department of Nuclear Medicine, Academic Hospital-Free University, Amsterdam, The Netherlands, 3Department of Surgery, Amsterdam Medical Centre, Amsterdam, The Netherlands

The first lymph node (sentinel node, SN) to receive lymphatic drainage from a primary tumour is the expected first site of lymph node metastasis. This SN concept has been validated for melanoma. Verification of the SN concept and the development of an accurate and simple technique of locating the SN will have enormous implications in the surgical management of breast cancer.

The aim of this study is to evaluate the SN concept in patients with breast cancer and whether the SN can be identified in the axillary drainage area using a handheld gamma probe after peritumoral injection of Tc99m-Tc-colloidal albumin. In 45 patients with T1 and T2 breast cancer and clinical negative axilla, lymphoscintigraphy was performed 2 and 18 hours after peritumoral tracer injection. Focal accumulations were registered and localised in vivo, using a handheld gamma probe. All patients underwent axillary lymph node dissection. From the surgical specimen the SNs were identified and separately send for pathological examination.

In all 41 patients lymphoscintigraphy revealed at least one distinct hot spot (SN) in the axillary region. In 8 patients more than one SN was visualised. In all 41 patients with scintigraphically identified SNs, radioactive lymph nodes could be retrieved from the axillary specimen. In this group in 29 (69%) both the SN and the axillary lymph nodes were without metastasis. Seven patients had metastasis both in SN and axillary lymph nodes (17%), and in 5 patients (12%) the SN was the only node with metastasis.

In the majority of breast cancer patients a SN can be identified after peritumoral injection of Tc99m-Tc-colloidal albumin and using a handheld gamma probe. In these 41 patients, the sensitivity and specificity of the radioactivity nodes showed 100% for predicting whether regional metastases had occurred. Statistical association between radioactivity nodes status and regional nodal status was highly significant (P<0.0001).

138. Routine axillary dissection for primary breast cancer in the elderly: a decision analysis

Nancy N. Baxter and I. G. Nagle
Departments of Surgery and Medicine, University of Toronto, Canada

Axillary dissection (AD) is routinely performed as part of the primary treatment of breast cancer. In the elderly, controversy over its routine use in all patients. In the elderly, where axillary nodal status is not integral to adjuvant therapy decisions, the main benefit of AD is the prevention of regional metastases. However, there is morbidity associated with the AD, which is considered necessary for proper orientation and to allow more accurate surgical re-excision. Although it has been demonstrated to be an accurate surgical procedure, which was recommended because traction may cause the wire to be moved or dislocated. In addition, 44% did not label the tumour specimen, which is considered necessary for proper orientation and to allow more accurate surgical re-excision. Although it has been demonstrated to be an unreliable technique for small non-palpable lesions, 11% of the surgeons still relied on frozen section examination. Of the pathologists, 79% appeared to be insufficiently informed by the surgeons whether the screen-detected lesion was palpable and whether microcalcifications had been seen on the mammogram.

Discussion: Guidelines, set up at a national level, need careful implementation and evaluation to change and improve clinical practice. At the start of a breast screening programme, it should be verified whether surgeons, pathologists and radiologists know the guidelines and have the skills to perform the techniques prescribed in the guidelines. We recommend the organization of regular, multidisciplinary meetings to prepare the diagnostic procedures and discuss possible treatment strategies for all women with non-palpable breast lesions.

140. How is the adherence in community hospitals to national guidelines for the work-up of non-palpable, screen-detected breast lesions?

A. C. Voogd1, J. M. Broekman2, M. A. Crommelin1, F van der Hors3, P. P. A. Raassen1, O. J. Repelaer van Driel4, J. A. Rookema1
1Comprehensive Cancer Centre South, Eindhoven, 2Department of Pathology, Beatrix Medical Centre, Den Bosch, 3Department of Radiotheray, Catharina Ziekenhuis, Eindhoven, 4Department of Radiotherapy, St. Mauritius Gasthuis, Venlo, 5Department of Surgery, Diaconessenhuis, Eindhoven, 6Department of Surgery, St. Elisabeth Ziekenhuis, Tilburg, The Netherlands

Introduction: Of all breast cancer patients detected at mass screening, the majority has asymptomatic, non-palpable lesions. Diagnosis and treatment of these lesions are complex and demand great skill and commitment from surgeons, radiologists and pathologists, especially with respect to interdisciplinary communication. In the Netherlands, a national screening programme was started in 1990, consisting of biennial screening for women between 50 and 70 years. Consensus guidelines were already developed and issued in 1988 by a few dedicated specialists, to assure high quality of the screening process and the diagnosis and treatment of non-palpable lesions detected by screening. The adherence to these guidelines in community hospitals was assessed.

Methods: A written questionnaire was sent to the surgeons (n=79), radiologist (n=67) and pathologists (n=22) in 17 community hospitals in the southeast of the Netherlands in 1995. The response rates were 78%, 75% and 86% respectively.

Results: In contrast to the guidelines, 11% of the surgeons did not have pre-operative localization of the non-palpable lesion performed on the day of surgery, which was recommended because traction may cause the wire to be removed or dislocated. In addition, 44% did not label the tumour specimen, which is considered necessary for proper orientation and to allow more accurate surgical re-excision. Although it has been demonstrated to be an unreliable technique for small non-palpable lesions, 11% of the surgeons still relied on frozen section examination. Of the pathologists, 79% appeared to be insufficiently informed by the surgeons whether the screen-detected lesion was palpable and whether microcalcifications had been seen on the mammogram.

Discussion: Guidelines, set up at a national level, need careful implementation and evaluation to change and improve clinical practice. At the start of a breast screening programme, it should be verified whether surgeons, pathologists and radiologists know the guidelines and have the skills to perform the techniques prescribed in the guidelines. We recommend the organization of regular, multidisciplinary meetings to prepare the diagnostic procedures and discuss possible treatment strategies for all women with non-palpable breast lesions.
detecting and in particular following the progress of metastatic disease including plain radiographs and bone scintigraphy. Osteocalcin, a 5.6kD protein is synthesised by osteoblasts and can be measured in plasma by an immunoradiometric assay. The aim of this study was to evaluate the use of this protein in the detection of bone metastases. Eighty-two patients with breast carcinoma (mean age 55 range 32-80 yrs) had serum osteocalcin measurements performed at 3 monthly intervals and a metastatic screen including chest X-ray, liver function tests and bone scintigram were performed whenever a clinical or biochemical suspicion of metastatic disease existed. There was no significant difference between T1, T2, T3 or T4 disease at presentation or between N0, N1 and N2 disease. Nineteen patients had bone metastases (mets) at presentation or developed bone metastases in the course of follow up.

<table>
<thead>
<tr>
<th>Table mean (SEM) osteocalcin in different categories of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>N0 mets</td>
</tr>
<tr>
<td>Bone mets (all)</td>
</tr>
<tr>
<td>1 hot spot</td>
</tr>
<tr>
<td>2 hot spots</td>
</tr>
<tr>
<td>≥3 hot spots</td>
</tr>
</tbody>
</table>

There was a positive correlation osteocalcin levels and CA15.3 (Pearsons correlation r = 0.3540, P = 0.002). This study confirms that serum osteocalcin levels may be used to monitor metastatic spread in breast carcinoma and may be useful in monitoring response to treatment.

142. Fenretinide inhibits breast tumour growth in vivo and in vitro

National Breast Cancer Research Institute, Department of Surgery, Dept of Pathology*, University College Hospital, Clinical Science Institute, Galway, Ireland.

The retinoids, a group of compounds structurally related to vitamin A, play an important role in cellular growth and differentiation. The effects of fenretinide (4-HPR), a synthetic retinoid, on MCF-7 (human) and RBA (rat) mammary adenocarcinoma cell-lines were plotted on growth curves for different doses of 4-HPR in vitro and the concentrations at which 50% of growth inhibition occurred (ED50) was calculated.

<table>
<thead>
<tr>
<th>Table % Growth as compared to control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose µmol/l</td>
</tr>
<tr>
<td>day 2</td>
</tr>
<tr>
<td>0.1</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>ED50</td>
</tr>
</tbody>
</table>

The ability of fenretinide to inhibit tumour growth in 3 day old Sprague Dawley rats injected with RBA (3 × 10^6 cells/50µL) was then studied. This concentration produced 100% tumour take within two weeks in 100 control animals. The tumour inhibitory potential of 4-HPR was assessed by feeding pregnant rats fenretinide (3mmol/kg) in the latter stages of pregnancy and while weaning. Tumour growth in 46 offspring (injected with RBA) was studied. This study confirms the ability of 4-HPR to significantly alter breast cancer growth in vivo and in vitro and has potential implications for chemoprevention and adjuvant therapy of breast cancer.

143. Immobilisation after axillary node clearance should be abandoned

D. J. Browse, W. A. Chapman, D. Goble, P. A. Jones
The Maidstone Hospital, Maidstone, Kent

67 patients with carcinoma of the breast were treated by lumpectomy and level three axillary node clearance between August 1994 and July 1995 in our Department. Immobilisation of the shoulder using a collar and cuff for ten days, was evaluated in this cohort to assess whether there was a significant reduction in either axillary wound drainage or the rate of seroma formation when compared with those patients without this restriction. Interviews with the patients also allowed an assessment of the acceptability of this regimen.

Axillary node clearance was performed through a vertical incision just behind the anterior axillary fold. The wound was drained by a 6mm suction catheter, left in place for 5 days irrespective of volume drained. 32 patients were randomised to the collar and cuff while 35 were allowed free arm movement and received physiotherapy. The two groups were well matched with regard to age (mean 57 years, range 43–74), number of nodes removed (15.5±0.5) and percentage with nodes involved by tumour (42%).

Wound drainage on days 3 and 4 was less with immobilisation of the shoulder, but reduction in total hospital drainage did not reach significance. The results for seroma formation were similar (31% following immobilisation vs. 43%; P = NS). Once a seroma had developed the clinical course was unaffected by the primary treatment, seromas resolving in 28–3 days. Patient interviews revealed that wearing the collar and cuff was uncomfortable and affected personal hygiene. Patients felt it delayed their return to normal activity and found that wearing a collar and cuff invited intrusive and unwanted enquiries.

Shoulder immobilisation following axillary node clearance does not significantly reduce seroma formation and was not acceptable to the patients. It should be withdrawn from the routine post-operative care of this group of patients.

144. Prognostic factors in node negative breast cancer

Clinica Oncológica 1-6º Piso, Instituto Português de Oncologia, Porto, R/D, Antonio Bernardino de Almeida, 4200 Porto, Portugal

Introduction: The nodal status in breast cancer is an important independent prognostic factor, being N0 a subgroup of patients of good prognosis. Despite that, twenty to thirty per cent of N0 have some type of recurrence at five years. In order to better understand this fact we decided to evaluate multiple prognostic factors of pN0 breast cancer patients.

Materials and methods: We have studied 150 consecutive cases primarily treated in our department between January 1983 and December 1990. We exclude the patients with age over 69 years, male patients and T4.

The overall survival and disease free survival were analyzed according to age, size, pt, surgical treatment, tumour grade and hormonal receptors status.

The survival curves were determined using the Kaplan-Meier method, and the statistical analysis applied were the log-rank and chi-square tests.

Results: The mean age was 52.7 years (range, 30–69). The distribution according to T was: T1—49.3%; T2—45.3% and T3—5.4%. The distribution according to tumour grade was: G1—26%; G2—38%; G3—14% and Gx—22%. Conservative surgery was accomplished in 29 (19.3%) patients; radical surgery was performed in the remainder (Madden—19.4%; Paty—54.0%; Halsted—7.3%). The hormonal receptor status was determined in 89 patients: estrogen receptors were positive in 83% of the cases; progesterone receptors were positive in 80.9%. The five years disease-free survival was 80.6%. The five years overall survival was 93.3%.

Conclusions: 1—in this group of N0 breast cancer patients, classical prognostic factors such as age, size, T, grading and hormonal receptor status have no statistically significant correlation with disease-free survival and overall survival. 2—N0 breast cancer patients constitute a group with excellent prognosis. 3—Axillary lymph node involvement remains the most important independent prognostic factor in localized breast cancer.

145. The impact of specialist breast services on the management of symptomatic breast cancer in North Wales

A. Al-Awa, J. Byrne, D. J. Crawford
Doctors’ Mess. Ysbyty Gwynedd, Bangor, LL57 2PW, North Wales, UK

Background: Recent data have suggested that patients undergoing investigation and treatment at a specialist breast unit have a significant
survival advantage over those treated at non-specialist units. The reasons are unclear. No studies have quantified how provision of specialist services alters management of symptomatic breast disease.

Aim: To assess the incidence of symptomatic benign and malignant disease in the 24-month period prior to appointment of a specialist breast surgeon in Gwynedd (1/8/89-31/7/91) and compare this to the most recent 24-month period (1/2/94-31/7/96).

Method: Pathology records for all Gwynedd residents undergoing breast surgery for symptomatic benign or malignant disease over the two time periods were retrieved.

Results: In 1989-91, breast surgery was spread evenly between 6 surgeons. In 1994-96, 96% of breast cancers and 93% of benign breast lesions were treated by a breast specialist. Conclusions: 1. There has been an apparent increase in the number of breast cancers treated in Gwynedd since 1989-91 (39.2%).

1.46. The contribution of the primary tumour to serum CA 15-3 levels in breast cancer

Departments of Surgery and Nuclear Medicine, University College Dublin and St. Vincent's Hospital, Dublin 4, Ireland

We have previously shown that serum levels of the glycoprotein antigen CA 15-3 at the time of diagnosis are strong independent prognostic markers in breast patients. However the biological mechanism underlying this observation remains unclear.

The aim of this study was to quantify tissue levels of CA 15-3 and clinical outcomes.

CA 15-3 concentrations were measured in homogenates of 123 breast tumours from patients without evidence of metastatic disease using a sandwich radioimmunoassay (CIB bio international, France, product code ELSA CA 15-3) and corrected for the protein content of the homogenates. A wide range of CA values was obtained (2 to 1431 units/ml protein). CA 15-3 levels were higher in more differentiated tumours (P=0.001, Kruskal-Wallis test) and in oestrogen-receptor tumours (P<0.001, Mann-Whitney U test). No relationship was observed between tissue levels of CA 15-3 and patient outcome in terms of either disease-free survival or overall survival (albeit serum CA 15-3 was a significant prognostic indicator in the population studied).

We conclude that the contribution of the primary tumour to serum levels of CA 15-3 is negligible. Serum levels of CA 15-3 are therefore a specific marker of occult metastatic disease in breast cancer patients.

1.47. Cosmetic and side effects after breast conserving surgery in primary treatment of early breast carcinoma

M. Brekajski, R. Drudic, N. Borozic, V. Posarac
Institute of Oncology and Radiology of Serbia, Belgrade

Background: Breast conserving surgery (BCS) is the optimal procedure in treatment of early breast carcinoma stage I and II. Selection of patients for BCS is related to tumour size <3cm in gross diameter, clinically axillary node negative. Treatment was either lumpectomy or quadrantectomy and axillary clearance level I-II and post operative radiotherapy external 45-50Gy. Adjuvant therapy was applied according to prognostic factors. The aim of the study was assessment of cosmesis and side effects after BCS and radiotherapy breast carcinoma stage I-II in a prospective study.

Method: In the period 1989–1993 there were 354 patients with BCS. Only 293 patients were eligible for study, which included prognostic factors, cosmetic effects, functional sequelae after BCS (criteria of EORTC Breast cooperative group).

Results: Mean age of group 54 years, premenopausal 111 (38%), postmenopausal 182 (62%) patients. Quadrant location of tumour in the breast was not a consideration. Surgical treatment: 140 (47%) patients had lumpectomy and 153 (53%) had quadrantectomy. Axillary clearance I-II was done in 241 (82%) and axillary clearance I-III level was carried out in 52 (18%) of patients. Pathological report: invasive carcinoma was diagnosed in 272 (92%) and 21 (8%) had non invasive carcinoma. 23 (8%) size T1, 181 (62%) T2, 89 (30%). We found 184 (63%) of patients without nodal involvement (N-) and 109 (37%) patients with nodal involvement (N+). Assessment of cosmetic effects and functional sequelae started after completion of therapy. Follow-up considered psychological aspects using qualitative and quantitative measurements. The results of psychological effects in BCS: excellent outcome 152 (51.8%), good outcome 96 (32.7%), poor outcome 45 (15.3%) of patients. Objective measurement showed cosmetic effects after BCS: breast symmetry 206, nipple asymmetry 31, breast deformity 42, breast edema 15, fibrosis of breast 24, telangiectasia 9 patients. Functional sequelae after BCS consisted of: skin inflammation 7, radiofibrosis 24, muscle paralysis 9, neuropathy 4, limited mobility of the arm 30 and lympheda 7 patients. Evaluation after BCS: median follow-up 47 months. Disease free interval for group is 47 months. Mean time to local recurrence was 37 months and distant recurrence, 65 months.

Conclusion: BCS provides radical primary treatment of breast carcinoma resulting in good prognosis. BCS also provides a favourable cosmetic result and small functional sequelae giving it an advantage over radical mastectomy.

1.48. Electron immunocytotoxic assay of ERF-B, P-glycoprotein, prolactin and HGF receptors in malignant breast tissues

I. E. Voloudakis-Baltatzis, M. Chisochou, A. Michailidou, K. Stavrelos
Dept. of electron microscopy-cell biology "G. Papankokou" Res. Center, Athens-GR

The monoclonal antibodies ERF-B, P-glycoprotein, prolactin and HGF were used to detect the presence and the distribution of these receptors in breast malignant and non-malignant tissues. A total of sixty breast tissues were examined, of which forty derived from malignant and twenty from non-malignant breast diseases. The presence and distribution of these four proteins show remarkable differences between malignant and non-malignant tissues. The ERF-B, P-glycoprotein, prolactin and HGF immunoreactivity was stronger in malignant than in non-malignant ones. Additionally, differences in the distribution and quantitative expression of these proteins, have been observed among malignant tissues from different patients depending upon the histological parameters of the disease (type and tumour grade, lymph node metastases). The electron immunocytotoxic assay in our research are considered as a powerful tool in the study of hormone mechanisms in breast cancer, knowing the crucial role of their expression.

In conclusion, our results demonstrate that these receptors could be used as additional markers, for the better understanding of human breast cancer.
150. Incidence and surveillance of breast cancer in Albania
C. Amanti, A. Lombardi, L. Regolo, A. Antonaci, G. Folliero, A. Mazrek,
R. Occhiato, M. Di Paola
University of Rome “La Sapienza” IVth Surgical Dept. Radiology *University
of Tirana

The Albanian population of around 3.5 million has been isolated from the rest
of Europe for almost 40 years, without a real industrial development. The incidence of breast cancer in Albania has been studied by
the University of Tirana during the period 1984–1986 on a series of 350 cases
with an annual average of 173 cases, 169 females and 4 males. Within Albanian
women, breast cancer represents 19% of all tumours, 24% excluding skin
tumours. Albania’s data, according to the standardisation over the world
population, reflect a state of low incidence (141/105). 70% of female population
in Albania is in the range of 0–34 yrs. The annual incidence of the urban areas
is 3.3 times higher than in rural areas (21.6 x 105 vs 6.4 x 105). These data are
derived from retrospective studies based on clinical observations because until
September 1993 there was no mammographic screening in Albania. In this period with
a grant of EU, we started a project regarding the study of incidence of breast
cancer in Albania. The study intends examining a sample of 6000 Albanian
women which corresponds to about 10% of Tirana’s population.

Publicity for the project was different from the usual system of recruitment
by letter. Publicity was at first done through the diffusion of scientific
information and presentation by television of what the project offered the
women. Women underwent a mammography and clinical examination. It is
remarkable that since mammography has been introduced in this country for
the first time none of the enrolled had ever undergone a mammographic
examination previously therefore this population must be considered as an
unexplored population. Mammography is performed in two views: mediolateral
and cranio-caudal. Processing and interpretation are performed on site. A
double reading of the mammograms is undertaken at a distance in Italy.

After the X-Ray examination doubtful cases underwent clinical examination,
supersound and FNAB if necessary. Until now 3000 mammographic
examinations have been performed and 30 cases of breast cancer found. Final
results after one year will be available by next September at the end of the study.

151. Quantitation of downstaging and dose intensity in locoregional
breast cancer after neoadjuvant chemotherapy
J. Shpakir, I. Kovalchuk, B. Bilynsky
Department Oncology, P.O. Box 2486, Lviv 290029, Ukraine

Neoadjuvant chemotherapy (NACT) represents a novel approach based on
modern theoretical, pharmacokinetic, and experimental principles. Between
March 1994 and July 1995, in Liviv Oncological Center NACT has been applied to 28 patients (ps) with operable breast tumours but too large for
immediate surgical procedure. Cytological diagnosis was provided by fine
needle aspiration. Hormone receptors were not evaluated. The median age
was 45 years (yrs) (range 29 – 69); 16 were <50 yrs; 12 were > or equal to
50 yrs. NACT consisted of 2–4 cycles (cy) of 2–5 drugs combinations:
 Cyclophosphamide (C), Methotrexate (M), Fluorouracil (F), Doxorubicin
(D), and Vinristine (V). The regimes were as follows: CMF+V+A or
AC+V. After NACT (one day before surgery or on day 29 of last cy
NACT) 528 (10.7%) pts had complete remission (CR) and 18/28
(64.3%)—partial remission (PR). Twenty-five pts (89.3%) had decrease
in T-stage after NACT: 10 had a I-IIa-stage decrease (T1 to T0, T1 to T0,
etc.), 13 a 2-stage decrease, 2 a stage-3 decrease. Eleven patients of (23 with N1+)
(47.8%) had change in N-stage (all I-N-stage decrease). Patients were analysed
separately according to the actual individual total dose intensity (TDI)
received. TDI of each study regimen was calculated as sum relative DI
pre- and postoperative lymphocyte counts between the two groups were
significantly different (P = 0.0075). Tumour response, as evaluated after NACT, was not associated with treatment TDI (r = 0.19, P = 0.33) in common group. Analysis shows a
slight, but, statistically significant correlation between TDI and response
for the premenopausal group (r = 0.54, P = 0.03) and no correlation for
postmenopausal group (r = – 0.07, P = 0.83). No statistical correlation has
been noted between response and tumour stage. No lethal toxicity was
observed. Conclusions: (1) NACT achieve downstaging in most
responders. (2) A statistically significant difference between young and elderly
patients in TDI receive was observed. (3) There was correlation between
TDI and response for premenopausal patients but not for older women.

152. Galactosylated anti-idiotype antibody leads to improved tumour
to blood ratios in mice bearing human breast carcinoma xenografts
N. Roche, C. Dean*, S. Eccles*, P. Carnochan* and N. P. M. Sacks
Section of Immunology and Physics, Institute of Cancer Research and Breast
Unit, St George’s Hospital

Currently the accurate assessment of axillary lymph node status in patients
with breast cancer requires axillary dissection. Alternative methods of
determining nodal involvement have been sought, such as
Radioimmunoassay (RIA). This involves the use of radiolabelled
monoclonal antibodies (Mab) to localise tumour. Previous RIA studies have
found that imaging is obscured by high levels of circulating background
radioactivity. We have developed a new technique of blood clearance using
galactosylated anti-idiotype Mab in order to improve the accuracy of RIA.

Anti-idiotype Mabs have a high affinity for bound circulating primary
Mab but low affinity for antibody bound to tumour. Galactosylation of
Mabs results in rapid hepatic clearance of the complexes. Administration of
galactosylated anti-idiotype Mab following the administration of labelled
primary Mab will result in binding and clearance of the excess circulating
labelled Mab.

In nude mice bearing bilateral MDA MB 361 breast cancer xenografts
the administration of galactosylated anti-idiotype Mab following localisation
of the primary Mab results in rapid blood clearance without early loss of
radioactivity. We have developed a new technique of blood clearance using
galactosylated anti-idiotype Mab in order to improve the accuracy of RIA.

As well as improving the accuracy of RIA this clearance technique can be
used in antibody directed therapy to reduce toxicity at sites distant to
the tumour.

153. Relationship of tumour stage and lymphocyte populations in
human breast cancer
A. Erolhlu, H. Canpinar, S. Cunlibel, E. Kansu
Ankara Oncology Hospital and Oncology Institute, Hacettepe University

Immunocompetence is common in patients with malignant disease. We
examined the influence of tumour stage on circulating lymphocyte
subpopulations in patients with breast cancer. Thirty-one women with breast
cancer who underwent surgical procedures at Ankara Oncology Hospital
between March and June 1995, were studied. Patients did not receive any prior
chemotherapy, radiotherapy, and they had no history of autoimmune disease.

Patients were staged by TNM classification and were divided into two groups:
Group 1 consisted of 15 patients with stage 2A tumour (T2N0Mo); Group 2
had stage 2B breast cancer (T2N1Mo). T- and B-cells were analyzed by flow
cytometry before the surgery and three weeks after the operation. Comparison
of pre- and postoperative lymphocyte counts between the two groups were
assessed by Wilcoxon matched-pairs test. In Group 2, there was a significant
preoperative increase in T suppressor cells and B1 cells, and a significant
decrease in ratio of T4/T8 compared to Group 1. In addition, significantly
derated ratio of T4/T8 and decreased T8 cells levels from preoperative values
were found in Group 2. This study suggested that tumour burden could be
associated with alterations in lymphocyte populations.

154. Morbidity from colonoscopy and screening for colorectal cancer
H. R. Dorrance, P. J. O’Dwyer
Department of Surgery, Western Infirmary, Glasgow, Scotland

Colorectal cancer is one of the commonest cancers in the Western world but
outcome has changed little in the last fifty years. Flexible sigmoidoscopy
and colonoscopy are now recommended for screening. There is likely to be
a wide variability in the population requiring full colonoscopy with estimates
ranging from 5–20%. In an effort to assess likely major morbidity from
colonoscopy, we reviewed all colonoscopies performed in one Unit over four
years. A total of 3572 colonoscopies were performed by five consultants,
surgeons and gastroenterologists. There were 12 perforations during this

time with an overall perforation rate of 1 in 300. Perforation rates among consultants varied from 1 in 50 to 1 in 1000. There were also two significant rectal bleedings and two major cardiac complications (one myocardial infarction and one episode of SVT) all requiring admission. We conclude that any screening programme for colorectal cancer using either flexible sigmoidoscopy or colonoscopy is likely to be associated with a high morbidity rate and mortality. This may jeopardize any potential benefit of such a screening programme.

155. Adjuvant chemotherapy after potentially curative resection of colorectal liver metastases

Th. Lehnerer, S. Vagiari, U. Hinz, Ch. Herfarth
Section of Surgical Oncology, Department of Surgery, University of Heidelberg, FRG.

Between 1981 and 1995 resection of colorectal liver metastases (LM) was performed in 286 patients. Primary tumours were located in the codon (n = 170) and rectum (n = 116). Median age of 178 men and 108 women was 60 years. Postoperative mortality following curative resection (n = 243) was 3.7 percent. Excluding postoperative deaths (n = 9) and patients with currently incomplete follow-up (n = 31) this analysis comprises 205 patients treated with curative intent. Five year overall survival of 205 patients was 25 percent, but only 14 percent (median 28 months) for the subgroup of patients receiving 5-FU-based adjuvant chemotherapy (n = 50).

To account for confounding factors multivariate analysis was performed. High grade of the metastasis (relative risk RR 1.87), synchronous metastasis (RR 1.68), margins <1cm (RR 1.6), intraoperative blood loss >21 (RR 1.6) and node positive primary tumours (RR 1.53) indicated poor prognosis (P = 0.007-0.026).

Patients were then allocated to three groups accounting for cumulative risk factors. Overall 5 year survival was 35, 17 and 0 percent for low, intermediate and high risk groups. When analyzed by adjuvant chemotherapy patients in the higher risk groups did not benefit and patients in the low risk group appeared to fare worse.

<table>
<thead>
<tr>
<th>risk group</th>
<th>relative risk</th>
<th>5 year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>chemotherapy (n = 50)</td>
<td>no chemotherapy (n = 155)</td>
<td>P =</td>
</tr>
<tr>
<td>low (n = 124)</td>
<td>1.0-2.99</td>
<td>19%</td>
</tr>
<tr>
<td>medium (n = 59)</td>
<td>3.0-4.69</td>
<td>19%</td>
</tr>
<tr>
<td>high (n = 22)</td>
<td>7.0-12.3</td>
<td>0%</td>
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</table>

These observations do not support the use of adjuvant chemotherapy after potentially curative resection of colorectal hepatic metastases outside clinical trial protocols.

156. Pitfalls of staging and quality control after preoperative radiochemotherapy of rectal carcinoma

O. Dworak, L. Keilholz, A. Hoffmann
Dept. of Pathology, Dept. of Oncology, Dept. of Surgery, University of Erlangen, Germany

Advanced rectal carcinomas may be suitable for preoperative radiochemotherapy achieving tumour reduction and operability. We examined seventeen patients with rectal carcinoma operated on after radiochemotherapy. All tumours were not resectable according to pretherapeutic staging by endosonography (US), computer tomography (CT) and clinical staging (Mason). The pathological work-up was more difficult after radiochemotherapy. Large area slides and step sections were frequently required to exclude small amounts of residual tumour. Four of six specimens with mucinous adenocarcinoma contained only single vital tumour cells in mucin residues. All but one specimen showed radiologic changes and tumour regression. The other cases exhibited different grades of tumour regression. In all specimens vital tumour cells or mass could be demonstrated. All but one specimen showed radiogenic changes and tumour regression. We performed in the presence of distant (lung) metastasis. Tumorous infiltration of the bladder trigonum and the urethra was regarded as a sign of metastatic involvement of locoregional lymph nodes were examined in all cases using special stains for basal membranes and vessels. Of 45 tumours with lymph node metastases, 42 (93%) had a low nm23-HI expression whereas only 35 of them were of high risk histology (G3, G4 or lymphatic invasion) (78%). Therefore nm23-HI expression within the primary tumour indicated lymph node status with a sensitivity of 93% and a negative predictive value of 91%. The classical pathohistological factors (high risk vs. low risk) had a sensitivity of 78% and a negative predictive value of 77% respectively.

Reduced expression of nm23-HI within primary colorectal carcinomas could serve as an additional independent marker in estimating the nodal metastatic potential of this tumour. The high sensitivity and predictive capacity of nm23-HI in estimating lymph node metastases justify further prospective clinical studies on larger series of patients.

157. The prediction of lymph node metastases in colorectal cancer by NM23-H1 and histopathologic variables

A. Tannapfel, A. Katalinic, F. Kieferling, Ch. Wittkekind
Dept. of Surgical Pathology1, Medical Statistics2 and Surgery3, University of Erlangen-Nürnberg, Germany

Spinchter-preserving surgical techniques have become established as an alternative treatment to abdominopelvineal resection for strictly-selected patients with colorectal cancer. In selecting patients, it is essential to determine before surgery which patient has microscopic spread to the perirectal and mesorectal lymph nodes and which do not. At present we can only predict the probability of nodal spread by accurately defining the resected local excision specimens according to depth of tumour infiltration, histological grade of differentiation and invasion of the lymphatic vessels.

To ascertain the risk of locoregional lymph node metastases from colorectal cancer we compared microscopic pathologic characteristics of the primary tumour with the expression of nm23-H1 protein. Loss or mutation of nm23-H1 has been correlated with high tumour metastatic potential and fatal outcome in colorectal carcinomas. The nm23-H1 expression of 100 colorectal carcinomas was analysed immunohistochemically at the time of primary curative surgery (R0 resection). Conventional histopathologic factors (depth of infiltration, grade of differentiation, invasion of lymph vessels or veins) which are proven indicators for metastatic involvement of locoregional lymph nodes were examined in all cases using special stains for basal membranes and vessels. Out of 45 tumours with lymph node metastases, 42 (93%) had a low nm23-H1 expression whereas only 35 of them were of high risk histology (G3, G4 or lymphatic invasion) (78%). Therefore nm23-H1 expression within the primary tumour indicated lymph node status with a sensitivity of 93% and a negative predictive value of 91%. The classical pathohistological factors (high risk vs. low risk) had a sensitivity of 78% and a negative predictive value of 77% respectively.

Reduced expression of nm23-H1 within primary colorectal carcinomas could serve as an additional independent marker in estimating the nodal metastatic potential of this tumour. The high sensitivity and predictive capacity of nm23-H1 in estimating lymph node metastases justify further prospective clinical studies on larger series of patients.

158. Multiple organ resections for locally advanced rectal cancer

A. Balogh, I. Zádai and Gy. Lázár
Department of Surgery, A. Sczenti-Gyorgyi Medical University, Szeged, Hungary

A total of 32 locally advanced rectal cancer cases underwent elective multiple organ resections, all with macroscopic clearance sufficient for curative "en bloc" resections. The surgery comprised abdominoperineal resection in 11 and an interior resection (Dixon) in 22 patients. Pelvic exenterations and heparcomorphoses were not carried out. The number of adjacent organs were affected by tumour and resected besides the cancerous rectum was two in 24 patients, and three or more in 8 patients. The rectal cancer was regarded as operable if the vagina (10 cases), adnexa (6 cases), vesicula seminalis (3 cases), small bowel (4 cases), bladder wall (3 cases), sigmoid (6 cases), major omentum (10 cases), sacral peristomeum (2 cases), prostate (2 cases) or ureter (2 cases) was involved, or if liver metastases (12 cases) had to be removed. In 12 cases, the macroscopically tumorous, additionally resected organs proved to be histologically negative. Multivisceral resections were not performed in the presence of distant (lung) metastasis. Tumorous infiltration of the bladder trigonum and the urethra was regarded as a sign of inoperability. 3 patients died, a mortality rate of 10%. In 2 of these 3, more than three organs were resected. The quality of life in the disease-free postoperative period was acceptable for 21 patients (70%).
159. Lectin binding is a predictor of poor survival in patients with colorectal cancer

Department of Surgery and *Department of Histopathology, University College London Medical School

The relationship between the tumour binding of the lectin, Helix Pomatia Agglutinin (HPA) and prognosis has been well documented in several human carcinomas but not in colorectal carcinoma. Its sugar specificity makes it an excellent tool in the investigation of the minor glycosylation changes known to occur in the metastatic cell. We therefore evaluated HPA binding as a predictor of survival in 120 patients (Dukes’ A: n=17, Dukes’ B: n=62, Dukes’ C: n=41) with ten year clinical follow-up who underwent curative resections for colorectal cancer between 1983–1985. Sections from formalin-fixed paraffin was embedded blocks were stained for HPA binding using the indirect immunoperoxidase method. They were graded by two independent observers as either positive or negative stainers, positive stainers being those where at least 5% of tumour cells stained strongly or 20% of tumour cells stained weakly.

Kaplan-Meier survival curves revealed a significant difference in survival between positive and negative stainers (p<0.0001). Risk estimates were obtained in a multivariate Cox’s Proportional Hazards model. The relative hazard of HPA positive staining versus HPA negative staining was 4.79 (2.85-8.04) and remained essentially unchanged at 4.31 (1.99-9.35) when adjusted for Dukes stage. These results indicate that HPA binding is a highly significant and independent predictor of poor survival in patients with colorectal cancer and could be used to identify a high risk group for careful surveillance.

160. Neutrophil-derived oxygen radical production is enhanced in colorectal cancer

Dept. of Surgery, University of Wales College of Medicine, Cardiff and *St. Mary’s Hospital Medical School, London UK

Colorectal cancer (CRC) is associated with an increase in circulating neutrophilia and a tumour leucocytic infiltrate, the significance of which is not fully established. Neutrophil-derived hypochlorous acid (PMN-HOCI), a long lived oxygen radical, may be involved in the host response to the tumour.

The rates of production of PMN-HOCI were determined in a consecutive series of 18 patients before and after surgery for CRC. There were 16 primary resections and 2 hemihepatectomies for liver secondaries. Fifteen patients undergoing surgery for non-malignant disease (NMD) acted as controls. PMN were obtained from blood using a discontinuous two-step centrifugation on ficoll-hypaque density gradients and PMN-HOCI production was subsequently determined by the taurocholinate method using UV spectrophotometry. All assays were performed in triplicate. The PMN-HOCI production is expressed as nmol/million PMN/min (control group) [0.393 nmol/million PMN/min (control group) P<0.05] (Mann-Whitney U test), decreasing to 0.611 nmol/million PMN/min [0.632 nmol/million PMN/min (control group)] on the tenth day, (P>0.05) (Mann-Whitney U test).

PMN in patients with CRC produce higher rates of HOCI than PMN in patients with NMD. This may be explained by increased levels of cytokines such as TNF. The PMN-HOCI production rate in CRC patients falls to levels comparable with those of patients with NMD postoperatively. Further studies are required to determine whether PMN-HOCI production can be used as a tumour marker and also as a prognostic indicator in patients with CRC.

161. Sphincter saving procedures in rectal cancer surgery: results of clinical experience

G. Nanni, G. Balduzzi, A. Scotti, G. Rosso, C. Botta, P. Demicheli, M. Duffara, E. Coppo
General Surgery Division S, Andrea Hospital, Verceil, Italy

Introduction: There is general agreement upon sphincter-saving procedures in the surgery for rectal cancer, in order to preserve an acceptable physiologic function. We compared the results of anterior resection of the rectum (AR), including (HPA) and intraperitoneal, and abdomino-perineal resection (APR).

Materials and methods: Between 1.1.1992 and 30.4.1995, 68 patients (pts) underwent surgery for rectal adenocarcinoma (M/F: 42/26, mean age: 68.5 years). Cancer site was proximal and middle (pme) rectum in 41 cases, distal (d) in 25 pts and in 2 cases of cancer recurrence after Hartmann’s resection (HR). According to Dukes classification 14 pts were stage A (21%), 17 B (25%), 17 C (25%) and 20 D (29%). Surgical procedures

were colorectal in 9 cases (because of poor conditions), HR in 8, APR in 17 (16 d. rectum, 1 recurrence after HR), APR (Knight-Griffins) in 34 (28 p/m. 5 d. rectum and 1 recurrence). APR was the selected procedure in 16/23 with cancer of d. rectum (64%); AR was performed in 28/41 (69%) pts with carcinoma of pme rectum. In 5/25 (20%) of d. rectum and 1 recurrence on rectal stump after HR. AR was the procedure of choice even in pts with cancer below 5cm from anal verge, but not invading perirectal tissues. In 4 patients surgical procedure included liver metastasis resection. All pts with stage C and D underwent adjuvant therapy: 5 FU + E A (Machover). 2 cycles. RT (Tot. 50 Gt). 5FU + FA. 4 cycles. pts with stage B2 and B3 and age >70 were treated only with RT.

Results: 2/17 pts (11%) died after APR. Complications encountered were 6 (9%), 3 (18%) APR and 3 (9%) AR. Mean hospital stay was 16 days (14–28) in AR and 17 days (13–30) in APR. Pelvic recurrence was observed in 3 cases: 1 APR (5%), 1 AR (3%) and 1 HR (1%). Two patients complained of incomplete evacuation: one of these had anastomotic stricture, which was dilated by endoscopic means. Follow-up results are still in progress.

Conclusions: APR is indicated only if AR is not technically feasible: this is not an oncologic but a technical limitation. Improvements in surgical technique and better complementary therapies do not alter survival, but significantly influence life quality of patients.

162. Cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) in peritoneal carcinosis of colorectal origin; a pilot study of 5 patients

Netherlands Cancer InstituteAntoni van Leeuwenhoek huis

Introduction: In 10% of patients with recurrence of colorectal carcinoma, only peritoneal metastasis can be found. Currently these patients are treated with systemic introduction of 5 FU/Lesuvorin, surgery is only used to palliate obstruction. With this treatment the median survival is less than 12 months. The mortality is predominantly caused by bowel obstruction and/or cachexia.

Rationale for Cytoreduction and HIPEC: Colorectal carcinosis is relatively resistant to chemotherapy. This resistance can be overcome by increasing the concentration and by additional hyperthermia. Intraperitoneal infusion of large molecules like Mitomycin C permits large doses to be given without any systemic toxic effects. This leads to a more effective anti-tumour activity after aggressive cytoreduction (tumour remnants <2.5mm).

Patient selection: Patients entered in this study, had proven peritoneal seedings of colorectal origin and no other metastasis on CT and Chest X-ray. They were fit to undergo therapy and were younger than 65 years of age.

Operation technique: Peritoneal metastasis were removed by stripping the peritoneal superficial layer, a technique pioneered by Sugarbaker et al. Furthermore, the removal of adhesions and necessary resections were also performed.

HIPEC: An in-flow Tenckhoff catheter was placed centrally in the abdomen, three outflow catheters were placed in the pelvis, the right and left subdiaphragmatic space, together with 3 temperature probes. The abdomen was covered with a plastic sheet, leaving an opening in the centre to allow the surgeon’s hand to stir the intestine. In- and outflow catheters were connected with perfusion machinery and a heat exchanger with reservoir. 3 litres of dialysis solution was heated (42–43°C) and infused at approximately 1 litre per minute into the peritoneal cavity. When the temperature in the abdomen reached 40–42°C, Mitomycin C (15mg/m²) was added to the circuit. 90 minutes of peritoneal lavage was performed.

Results: 5 Patients, all male with a mean age of 53 years (range 39–64 yrs), were treated in this pilot study. In all cases a complete cytoreduction to the surgical procedures performed. Duration of postoperative ileus could be carried out. The peripheral temperature could be maintained at 40°C (39–42°C). The pharmacodynamics of Mitomycin C were determined in perfusate, plasma and urine and supported a clear advantage in the AUC-ratio for the intraperitoneal application of Mitomycin C. No major postoperative complications occurred. Minor morbidity was primarily related to the surgical procedures performed. Duration of postoperative ileus (resuming of soft diet) was 9 days (5–13). Mean period of hospitalization was 19 days (range 15–23).

Conclusion: Cytoreduction combined with hyperthermic intraperitoneal Mitomycin C can be performed with acceptable morbidity and without systemic toxicity in excess of grade 2 (WHO). However, further study on overall survival is needed.
163. Intensive follow-up after curative resection for colorectal carcinoma: Is it worthwhile?
M. Sailer, M. Kraemer, R. Leppert, K.-H. Fuchs, A. Thiede
Chirurgische Universitatsklinik Würzburg, Josef-Schneider-Str. 2 97080 Würzburg, Germany

The routine follow-up of patients following resection for colorectal carcinoma requires considerable financial and manpower resources. Furthermore, some investigations (e.g. colonoscopy) are unpleasant for the patient and carry their own morbidity. The goal of follow-up programmes is an early detection of tumour recurrence so that patients can be submitted to further surgery with the greatest chance of cure. However, it has been criticised that despite a complete follow-up and early intervention the final outcome in terms of survival does not differ significantly compared with patients without follow up. Since the late seventies most patients in Germany are offered a follow-up programme after potentially curative resection of their colorectal carcinoma. The schedule comprises a set of investigations (blood tests including CEA, Ca 19-9, endoscopy, CT-scan, endosonography. Chest X-Ray) at certain intervals (3-monthly the first two years, then 6-monthly up to 5 years). The aim of our study was to establish the outcome of all patients who has a complete follow-up in order to evaluate the benefit of the programme.

Methods: At the University Hospital of Würzburg/Germany all cancer follow-up data have been entered prospectively in a computer since August 1986. We analysed the data of all patients who had undergone primary surgery for a colorectal carcinoma at our institution until December 1992 and who had then been followed up according to the above mentioned schedule (up to December 1992 and who had then been followed up according to the above mentioned schedule (up to December 1995, thus with a minimal follow up of three years).

Results: Of 454 patients (271 colon, 183 rectum) 382 (84%) were operated upon with a curative intention. 57 (15%) (22 colon, 35 rectum) had a recurrence of their primary tumour within the study period. Of these 167 (28%) patients underwent further surgery with a curative intention, of which four patients are alive tumour-free, six had further early recurrence and died and the remaining four had further salvage surgery for re-manifestation of the disease. Only one patient of the latter group is alive tumour-free. In summary, only five patients (8.8%) with a recurrence profited from further therapy in terms of prolonged survival. Only two of them were asymptomatic but had pathologic follow-up investigations, whereas the other three had symptoms at the time of diagnosis.

164. A safe technique for cure of superficial rectal carcinomas and adenomas: transanal endoscopic microsurgery (TEM) compared to the gold standards
G. Windel, K. W. Schmid, R. Herwig, B. Reers
Dept. of General Surgery, Dept. of Pathology of the Westfalische Wilhelms-University of Münster, Germany

Purpose: Prospective randomized study local resection using TEM with anterior resection for early rectal carcinomas (uTI N0 gastro, low risk) and with peranal submucosal excision for sessile adenomas.

Randomized distribution to the operative techniques was done after endoluminal ultrasound staging. Procedures were transanal endoscopic microsurgery (acc. to Bues), deep anterior resection (AR), peranal submucosal excision. Patients with T1-carcinoma: n=25 (TEM) versus n=28 (AR); adenomas: n=98 (TEM) versus n=90 (PSE).

No significant difference in age and sex and intraluminal distribution of the tumours was observed between the groups. Evaluation for blood loss, operation time, hospitalisation, analgesic demand, early and late morbidity, mortality, recurrence, five year survival (carcinomas only) were assessed. All procedures were performed under general anaesthesia.

Results: Comparing TEM with AR, three patients were excluded as a result of histopathological reports (pT3). Significant differences of TEM to AR were found for blood loss, operation time, hospitalisation time and anesthetic demand (ANOVA, Student-Newman-Keuls test P<0.001). Perioperative mortality was zero, early and late complications of TEM (20%) differed markedly from AR (35%). No difference in five year survival probability rates between TEM and AR was noted (95.8% vs. 96%, hazard ratio 1.002, log rank test), mean follow-up was 41 months for TEM and 45 months for AR. Local relapse of TEM was found in 4% of the carcinomas and was due to fistula or abscesses were not observed.

Conclusions: The comparison of the most precise transanal procedure (TEM) has distinct advantages in surgery for sessile adenomas concerning morobidity and local failure rates. Local excision for rectal carcinomas showed similar survival rates compared with anterior resection, if endoluminal ultrasound is used for staging and strictly low risk tumours are selected. The TEM technique with lower local failure seems beneficial to patients and justifies the difficult technique of TEM.
168. Endorectal ultrasound in the follow-up of rectal cancer

R. Lepper, M. Kraemer, M. Sailer, D. Bassen, M. Graf, K.-H. Fuchs, A. Thiede
Chirurgische Klinik der Julius-Maximilians-Universität, Josef-Schneider-Str.2, D 97070 Würzburg (Germany)

Since 1993 more than 900 endorectal sonographic examinations were performed at the Department of Surgery, University Hospital Würzburg. During that time endorectal ultrasonography (ERUS) has gained increasing importance in the follow-up of patients who underwent anterior resection for rectal cancer. ERUS is particularly useful in identifying submucosal and extrarectal local recurrences, since resolution is higher than CT-scan and comparable only to magnetic resonance imaging, which is considerably more time-consuming and expensive. Attempts at curative therapy of local recurrences require earliest possible detection. This may be achieved by comparing standardized endosonographic images at regular follow-up examinations with images recorded 6 months postoperatively, when the formation of scar tissue usually has been completed. Apparent changes in the region of the anastomosis after 6 months or the new appearance of submucosal or extrarectal lesions, which frequently escape endoscopic detection, are highly suspicious of recurrence. Endosonographically-guided biopsies are then taken, which permit the precise placement of biopsies under visual control with a deviation of less than 1 mm. With this method, so far 12 local recurrences were confirmed, 8 of them extramural. In 4 of the cases a CT-scan performed at the same time did not show any signs of local recurrence.

We present a standardised follow-up program with ERUS. At times of increasing economical pressures in health care ERUS remains an inexpensive, relatively easy to learn, and effective diagnostic tool with good patient acceptance. It is therefore an useful adjunct in the follow-up of patients with rectal carcinoma.

169. P53 expression in node-negative colorectal cancer

A. Tsujibas, Y. Anno, K. Anzai, Y. Kikuchi, T. Yoshida, R. Abe
Dept of Surgery, Fukushima Medical College, Fukushima 96012, Japan

Aim: To elucidate the tumour aggressiveness in node-negative colorectal cancer, immunohistochemical p53 was investigated as a prognostic factor.

Materials and methods: The expression of p53 in formalin-fixed paraffin-embedded sections from 66 colorectal cancer between 1983-92 was immunohistochemically stained using DO-7. Tumours which exhibited 10% or more nuclear staining were considered as positive. A correlation between p53 expression and histopathological variables, DNA ploidy and survival was investigated.

Results: p53 was demonstrated positively in 26 (39.4%) of 66 cancers. No correlation was found between p53 and histological differentiation, site, Dukes' stage and DNA ploidy. There was no difference of survival between patients with p53(-) and p53(+). DNA ploidy showed that diploid cancer has a trend for good survival. Grading by p53 and DNA ploidy has no prognostic value for prognosis.

Conclusion: Although the sample size was limited, we could not find that p53 expression was a useful for predicting the survival in patients with node-negative colorectal cancer.

170. Oncologic results from coloanal anastomosis for low rectal carcinoma

Department of Surgery, Taichung Veterans General Hospital, Taiwan, R.O.C.

Sixty-two patients treated for primary rectal carcinoma by low anterior resection with coloanal anastomosis between 1983 and 1995 were studied retrospectively. There were 43 men and 19 women. The median age was 58 years (range, 23 to 79 years). The distance from the anal verge to the lowest edge of the tumour ranged from 4cm to 9cm, with a median distance of 6cm. One (a 67 years old patient) had Dukes' A tumour, 31 (50%) were Dukes' B, 26 (42%) were Dukes' C, another 4 underwent palliative resection. There was one operative mortality. Clinical anastomotic leakage occurred in 18% (handsewn 19%, stapled 17%). Mean follow-up is 68 months. Among the patients who underwent curative resection, the incidence of local recurrence was 21%, and the overall 5-year survival rate was 70%. The five-year survival rate was 83.4% for Dukes' B, 63.4% for Dukes' C (P=0.17). The 5-year disease-free survival rate was 64.3%. The 5-year disease-free survival was 80.6% for Dukes' B, 46% for Dukes' C (P=0.0032).

171. The ultralow resection of rectal cancer as an alternative for abdomino-perineal amputation

G. Kolbert, H.-P. Bruch, G. Miller, A. Herold
Department of Surgery, Med. University of Luebeck/Germany

Ultralow resection of rectal cancer in the distal third of the rectum is an accepted spinesaversing method. From December 1990 through December 1995 42 patients, 17 women and 25 men, with a mean age of 62.7 years had an ultralow resection of the rectum at our institution.

We had 15 carcinoma stage Dukes A, 9 carcinoma stage Dukes B, 14 carcinoma stage Dukes C and 4 carcinoma stage Dukes D. In 18 patients we carried out a transanal suture anastomosis, in 24 cases a stapled anastomosis.

We had a mortality rate of 2.5% and an anastomotic stapled leakage rate of 14%. In 4 cases of anastomotic leak we carried out a transanal resuturing. In 3 cases we saw a rectovaginal fistula, once after a spontaneous perforation, and twice after adjuvant radio-therapy. The mean resting pressure of the sphincter 14 days operation was 63mmHg compared with 88mmHg pre-operatively. The mean squeeze pressure preoperatively was 151mmHg and postoperatively 110mmHg. 34 of the 42 operated patients were fully continent, 4 were partial incontinent and 4 fully incontinent.

The mean follow-up was 19.6 months. 13% of the patients had a follow-up of 3 years. All patients operated in stadium Dukes A or B were free of recurrent cancer till now.

We conclude that ultralow resection of rectal cancer is a good alternative to rectal amputation for treatment of rectal cancer with similar results in the follow-up and a better quality of life.

172. Replacing hepatic artery catheters—is it worthwhile?

J. C. Doughty, G. Keelh, C. S. McArdle
University Department of Surgery, Glasgow Royal Infirmary

In patients with colorectal liver metastases impressive response rates have been reported using regional chemotherapy. The survival of implanatable silicone catheters is approximately 12 months. A problem arises in patients with hepatic artery catheters the catheter occluded in 17 patients at a time varying from 1 to 12 months. The mean duration of survival with silicone catheters is approximately 12 months. A problem arises in patients with hepatic artery catheters the catheter occluded in 17 patients at a time varying from 1 to 12 months. The mean duration of survival with silicone catheters is approximately 12 months. The mean duration of survival with silicone catheters is approximately 12 months. The mean duration of survival with silicone catheters is approximately 12 months.
Carcinomatous peritonitis is not necessarily present. Longterm survival after cancer the primary aim must be to overcome the vital threat of perforation months (2-9). respectively.

After non curative resection (median and range): 44 months (20-103) and 4 distant metastasis were present in 3 of 19 patients. Postoperative mortality was oncorologic resection should be performed in 38 patients (64%) underwent total gastrectomy with or without D2-lymphadenectomy. The resectability rate was 75%. 34/61 cases were classified as advanced (stage III and IV according to UICC), early cancer was found in 20 cases. The 5-y-survival rate was 21% for all patients. In cases with lymph node metastases 5-y-survival went down to 10% (n=1) resp. median survival of 8 months (n=3).

We conclude that beside systemic endoscopy a radical approach in operation technique including D2-lymphadenectomy or multivisceral resection is necessary.

174. Results after surgical therapy of perforated gastric cancer
G. Timmermanns, K. Buhl, Th. Lehnert, Ch. Herfarth
Dept. of Surgery, University of Heidelberg, Germany
Perforation of the stomach due to cancer is a rare complication. Perforated gastric cancer (PGC) is therefore frequently misinterpreted as a perforated peptic ulcer.

Of 177 patients with gastric cancer surgically treated at our department between 01/1982 and 01/1996, we found 19 patients (1.6%) with a PGC. Median age was 73 years (range 31-90 years); sex ratio: 7 male to 12 female patients. The diagnosis of gastric cancer was preoperatively known in 3 patients. 14 patients were admitted to our department with an acute abdomen. Of II77 patients with gastric cancer surgically treated at our department 28 patients were found to be unresectable at operation. 29 underwent early elective operations in 2 patients. The perforation of the gastric cancer was located in the antrum (n=12), abdominal aortic aneurysm (n=1) and acute cholecystitis (n=1). One patient was admitted with upper gastrointestinal bleeding. Iatrogenic perforation after gastroscopy was diagnosed in 3 patients.

The perforation of the gastric cancer was located in the antrum (n=12), corpus (n=4) and cardia (n=3). Emergency operations had to be performed in 17 patients, early elective operations were performed in 2 patients. The following surgical procedures were performed: local repair (n=10), distal gastrectomy (n=7) and total gastrectomy (n=2). In a second operation, histologically proven gastric cancer, a total gastrectomy with lymphadenectomy was performed in 5 patients. Because of accompanying inflammation the tumour stage was frequently overestimated intraoperatively compared to the pathological report. We found pT2 (n=7), pT3 (n=8), pT4 (n=1) (in those cases that were resected). At the time of the first operation distant metastases were present in 3 of 19 patients. Postoperative mortality was high (n=8; 42%) due to a high preoperative morbidity of 63%. Postoperative survival (n=11) was much better after curative (oncologic) resection than after non curative resection (median and range): 44 months (20-103) and 4 months (2-9), respectively.

Old age and a poor general condition in these patients are the reasons for the high postoperative mortality. Therefore in cases of perforated gastric cancer the primary aim must be to overcome the vital threat of perforation complications and to prove the carcinoma histologically. In a second step oncologic resection should be performed. After perforation of gastric cancer, carcinomatous peritonitis is not necessarily present. Longterm survival after

175. Surgery of gastric stump carcinoma—a question of radicality
J. R. Kocik, H. St. Nettberg, J. Brockmann, T. Berns
Klinik und Poliklinik für Allgemeine Chirurgie der Westfälischen Wilhelms-Universität Münster
The results of a retrospective analysis of cases of carcinomas of the gastric stump are presented. Between January 1984 and December 1994 a total number of 61 patients were operated. Mean age of the patients was 62.9 years, the male/female ratio was 6:1. In 59/61 patients the original operation performed was a Billroth-II-resection. 39 patients (64%) underwent total gastrectomy with or without D2-lymphadenectomy. The resectability rate was 75%. 34/61 cases were classified as advanced (stage III and IV according to UICC), early cancer was found in 20 cases. The 5-y-survival rate was 21% for all patients. In cases with lymph node metastases 5-y-survival went down to 10% (n=1) resp. median survival of 8 months (n=3).

We conclude that beside systemic endoscopy a radical approach in operation technique including D2-lymphadenectomy or multivisceral resection is necessary.

176. Modern anti-ulcer medication and gastric carcinoma—is there a delay in definitive treatment?
N. T. Corrigan, M. G. O’Riordain, F. Kenny, G. McEntee
Mater Misericordiae Hospital, Eccles St., Dublin 7
With the advent of potent anti-peptic ulcer medications as well as the free availability of flexible endoscopy, patients with gastric ulcers are increasingly treated medically rather than being referred for early surgery. To determine whether this may lead to a delay in the diagnosis of gastric cancer, we retrospectively reviewed 100 consecutive cases of gastric carcinoma diagnosed in our institution in a 5 year period 1991–1995.

The median age of the study group was 72 yrs (range 38–92), 61% were male. The commonest presenting symptom was dyspepsia (64%) followed by weight loss (31%), anaemia (27%) and anorexia (18%) and hematemeses (12%). The median duration of symptoms prior to diagnosis was 5.5 months (1 day to 20 years). Ninety-nine patients had adenocarcinoma and one lymphoma. Fifteen percent of tumours were stage I, 5% stage II, 6% stage III and 74% stage IV. 64% were poorly differentiated or undifferentiated. Twenty-four patients were considered inoperable and the remainder underwent surgery. Of these, 28 patients were found to be unresectable at operation. 29 underwent a partial gastrectomy, and 19 had a total gastrectomy. Follow-up data were available in 89 patients, and the median survival in these patients was 15 months by life table analysis.

Almost half (48%) of patients received anti-ulcer treatment prior to diagnosis and of these, 27 patients were treated for greater than 3 months (median 8 months). Treatments included H2 antagonists (33%) and proton pump inhibitors (14%). In two of these cases the mucosa had healed over a malignant ulcer. In 14% of cases at least one previous endoscopy had failed to demonstrate tumour. In these patients the median duration between the first endoscopy and diagnosis was 10.5 months (range 1 month–11 years).

A significant proportion of patients diagnosed with carcinoma of the stomach have had long term anti-ulcer treatment or serial endoscopic surveillance prior to diagnosis. More prompt referral for surgical resection may well lead to the diagnosis of cancer at an earlier stage.

177. Gastric carcinoma, pre-intra and postoperative staging
C. Farberios, A. Nikolaou, D. Nikolaou, M. Katsoulis, J. Lekka, J. Kappas, A. Arvelakis, B. Lissas
1st Surgical Department, Mater Misericordiae Hospital, Piraeus
We compared patients with malignant tumours of the stomach, preoperative (combined clinical and radiological staging and endoscopic Borrmann classification), intraoperative (by the surgeon; stage I to IV), and
postoperative staging including histological results (pTNM) in respect of resectability and prognosis.

All patients with adenocarcinoma of the stomach were staged during the hospitalisation by the different specialists. Out of the 112 patients with malignant tumours of the stomach 84 were finally evaluated for the study. We excluded 28 patients with other malignancies or with a follow up of less than 4 months. Preoperative endoscopic Borrmann classification was done by the gastroenterologist, intraoperative classification by the surgeon and postoperative by the pathologist.

Results: Preoperative staging was unreliable and there was no relationship between postoperative postoperative staging nor survival. However, intra- and postoperative staging correlated significantly between the different groups and with survival (P<0.001).

In conclusion, the results indicate that preoperative staging systems are not yet reliable, although this may improve with the development of endosonography. All operable patients with gastric carcinoma should undergo a laparotomy because on a possible curative resection. Patients with stages I-III should be resected radically with complete dissection of lymph node compartments I and 2, with a minimal hospital mortality (4%).

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Results: Preoperative staging was unreliable and there was no relationship between postoperative postoperative staging nor survival. However, intra- and postoperative staging correlated significantly between the different groups and with survival (P<0.001).

In conclusion, the results indicate that preoperative staging systems are not yet reliable, although this may improve with the development of endosonography. All operable patients with gastric carcinoma should undergo a laparotomy because on a possible curative resection. Patients with stages I-III should be resected radically with complete dissection of lymph node compartments I and 2, with a minimal hospital mortality (4%).

We concluded that this technique has no related morbidity and is useful in the identification of the different groups of lymph nodes and so increases the number of lymph nodes dissected (mean 29.3 lymph nodes) when compared with historical data.

180. Intraoperative lymphangiography in gastric cancer with micro carbon: a pilot study
A. S. Matos, L. Santos, C. Lopes, G. dos Santos
Instituto Portugues De Oncologia Francisco Gentil Centro De EORTC, Rua Dr. Anxão Bernardino De Almeida, 4200 Porto, Portugal
As reported by the Japanese studies, the lymphadenectomy (D2) in gastric cancer (Stage II and III) cases the overall survival and disease-free survival. The number of lymph nodes dissected by some authors by adequate D2 lymphadenectomy is 25.

In the Surgical Oncologic Clinic at the Portuguese Institute of Oncology, Oporto we began performing intraoperative lymphangiography with micro carbon, in order to standardise the gastric lymphadenectomy. This study was performed in 10 patients with the objective to determine the feasibility or the technique and the effects. The results in terms of number of lymph nodes dissected are shown in the following table:

<table>
<thead>
<tr>
<th>Case</th>
<th>Type of surgery</th>
<th>Lymph node (&lt;3cm)</th>
<th>Lymph node (&gt;3cm)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>STG</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>STG</td>
<td>11</td>
<td>11 (1)</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>STG</td>
<td>14</td>
<td>11 (1)</td>
<td>25 (3)</td>
</tr>
<tr>
<td>4</td>
<td>TG</td>
<td>30 (4)</td>
<td>9 (2)</td>
<td>39 (6)</td>
</tr>
<tr>
<td>5</td>
<td>STG</td>
<td>25 (4)</td>
<td>21</td>
<td>46 (4)</td>
</tr>
<tr>
<td>6</td>
<td>STG</td>
<td>14 (4)</td>
<td>10</td>
<td>18 (4)</td>
</tr>
<tr>
<td>7</td>
<td>STG</td>
<td>24</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>TG</td>
<td>8</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>9</td>
<td>STG</td>
<td>28</td>
<td>9</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td>STG</td>
<td>14</td>
<td>11 (3)</td>
<td>25 (3)</td>
</tr>
</tbody>
</table>

*Distance between lymph node and tumour, ( )=lymph node invasion.
TG = total gastrocytomy, STG = subtotal gastroctomy

We concluded that this technique has no related morbidity and is useful in the identification of the different groups of lymph nodes and so increases the number of lymph nodes dissected (mean 29.3 lymph nodes) when compared with historical data.

181. Less immune and stress reaction and improved postoperative recovery after laparoscopic colon resection in the rat
Chr. Kuntz, A. Wunsh, F. Glaser, M. Aulmann, Ch. Herfarth
Surgical Department, University of Heidelberg, Germany
To investigate the difference between laparoscopic and open bowel surgery, the stress and immun reaction as well as the postoperative body weight were measured in 22 rats having laparoscopic or open colon resection or anesthesia only.

Corticosteron, H1 beta. Neopterin and body weight were measured directly before and after operation as well as 1 day and 1 week later. 10 rats had been operated by laparoscopic colon resection and 10 by open colon resection. 2 had only anesthesia.

Directly after open operation Corticosteron increased from 338ng/ml to 665ng/ml, after laparoscopic procedure to 512ng/ml. Neopterin increased from 0.210 to 0.397ng/ml in open and to 0.221ng/ml in laparoscopic operation. H1 beta increased to 330 in open and to 100 in laparoscopic surgery. After open surgery rats lost 2% body weight one week after operation, laparoscopic operated rats increased of 1.7% in weight. Under anesthesia, there was no significant changes of the parameters. Operation time was 25 min in laparoscopic and 30 min in open surgery.

This study indicates that laparoscopic colon resection is associated with less stress (Corticosteron) less alteration of immun system (Neopterin, H1 beta) and improved postoperative recovery (body weight).

182. Combined preoperative irradiation and local hyperthermia delays early healing of colonic anastomoses in rats
J. Biert, Th. Wobbes, W. Sefter, B. de Man, J. Hoogenhout, Th. Hendriks
Department of General Surgery and Surgical Oncology, University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands
Application of hyperthermia is a most promising method to increase the efficacy of radiation therapy. To determine if a combination of preoperative irradiation and local hyperthermia of a colonic segment is detrimental on subsequent early anastomotic healing we designed an animal experiment. 80 male Wistar rats were randomly divided into four groups. In each
animal, a segment of the colon was treated successively by (sham-)irradiation and (sham-)hyperthermia. After 5 days a colonic resection was performed with construction of an anastomosis: the distal limb consisted of (sham-)irradiated, (sham-)hyperthermia-treated bowel. Rats were sacrificed 3 or 7 days after surgery.

Results: all animals tolerated (sham-)irradiation well. Weight was diminished, though not significantly, in treated animals as compared to the control group. After combined preparative irradiation and hyperthermia the frequency of local anastomotic complications increased: 4 animals (out of 20) had a covered perforation at sacrifice. In this group the bursting pressure was lowered 3 days after the operation ($P=0.0078$). Breaking strength was also lower, but not significantly. Serum albumin level was significantly lower as compared to the control group ($P=0.0056$); serum protein level was not decreased. After 7 days there were no differences between groups. Anostomotic hydroxyproline content of the anastomotic tissue was significantly higher in rats treated with radiation plus hyperthermia compared to control rats (in both 3-days and 7-days groups). Anostomotic hydroxyproline concentration showed no differences between groups.

Conclusion: the combination of preparative irradiation and hyperthermia results in increased local anastomotic complications. Anastomotic strength is at risk in the first days after the anastomotic reconstruction. Preparative irradiation or hyperthermia alone does not lead to impaired anastomotic healing in the early phase.

183. Tumour cells will adhere to laparoscopic ports

H. R. Dorrance, P. J. O'Dwyer
Department of Surgery, Western Infirmary, Glasgow

Port site metastases are a worrying complication of laparoscopic surgery for colon cancer. The cause of these lesions remains unknown. Adherence of tumour cells to instruments and ports may play a significant role. The aim of this study was to assess the rate of cell adherence using commonly used laparoscopic ports, in a laboratory setting.

Four types of 5mm port were studied: a stainless steel reusable, Tristar 5mm (Ethicon Endo-Surgery, U.K.), Surgiport 5mm (Autosuture) and Apple 5mm (Medical Europe). Melanoma cells were labelled with ["3H"]-lodo-2'-deoxyuridine and suspended at 2 x 10{sup 7} cells per ml. Ports were incubated in this suspension for one hour at 37°C. Ports were then washed twice in cold phosphate buffered saline. Gamma radioactivity was counted using a gamma counter (Compugamma, LKB-Pharmacia). The median counts per minute for each port were: reusable 1156 (IQR 500.5-1888.125), Tristar 1017.75 (IQR 664.75-1304.5), Surgiport 427 (IQR 185-1489.5). Apple 741.75 (IQR 557.75-1319.4). One million labelled cells had a median count of 24180 cpm (IQR 20518-29411). Therefore, a mean of 34 540 cells were adhering to each port. The number of adherent cells was not significantly different between groups. The aim of this study was to assess the rate of cell adherence to commonly used laparoscopic ports and may play a part in the pathogenesis of port site metastases.

184. Lipopolysaccharide in air may account for acceleration of tumour growth after laparotomy

M. L. Da Costa, H. P. Redmond, D. J. Bouchier-Hayes
RCsI Department of Surgery, Beaumont Hospital, Dublin 9

We have previously shown that laparotomy and laparoscopy differentially accelerate tumour growth in the early post-operative phase, and postulate that lipopolysaccharide in air may be in part responsible for this. The aim of this study was to evaluate the effect of laparotomy, laparoscopy and LPS (lipopolysaccharide) on tumour growth in a murine model. Study 1: C57BL/6 female mice (n=25) received right flank injections of 1 x 10{sup 5} B16 melanoma cells. When tumours became palpable they were randomised into control (Con: anaesthetic only), laparoscopy (Lpy), laparotomy (Lpt), Air Laparoscopy (AL), and i.p. LPS (45ng given at day 0) groups. Study 2: Tumour-bearing C3H/HeN (LPS-sensitive) and C3H/HeJ (LPS-resistant) mice (n=10 each group) underwent the former three procedures. In both studies the tumours were measured and flank tumour volume (FTV) calculated every other day for ten days thereafter. Data expressed as mean ± sem. Study 1: *P<0.05 wrt to Con; **P<0.05 wrt Lpy; ***P<0.002 Lpt HeN vs all gns; $P<0.05 Lpy HeN vs Con HeJ; #P<0.05 Lpy HeN vs Lpy HeJ; $P<0.05 Lpt HeN vs Con HeJ & Lpy HeJ. Analysis by ANOVA with LSD post hoc correction. Study 1: Tumour growth increased significantly in all groups compared to Con at day 2 but only significantly in groups with LPS contamination of the peritoneum compared to Lpy and Con at day 4. Over the next four days there was no significant increase in FTV between the groups, however at day ten, there was again another significant increase in FTV in the Lpt. AL and LPS group compared to Con and Lpy. Study 2: demonstrates a markedly significant increase in tumour growth in LPS-sensitive mice after laparotomy compared to all groups at days 2 and 4. Thus exposure of the peritoneal cavity to small concentrations of LPS as present in room air appears to stimulate tumour growth in the early post-operative period.

\[
\begin{align*}
\text{Mean DDFTV/cm}^3 & \text{(Study 1)} \\
\text{Day} & \text{2} & \text{4} & \text{10} \\
\text{Con} & 0.08 \pm 0.015 & 0.18 \pm 0.036 & 0.29 \pm 0.035 \\
\text{Lpt} & *0.34 \pm 0.049 & *0.43 \pm 0.054 & *0.45 \pm 0.035 \\
\text{Lpy} & *0.25 \pm 0.023 & *0.20 \pm 0.023 & 0.27 \pm 0.031 \\
\text{AL} & *0.40 \pm 0.067 & *0.39 \pm 0.045 & *0.42 \pm 0.039 \\
\text{LPS} & *0.23 \pm 0.023 & *0.41 \pm 0.024 & *0.44 \pm 0.048 \\
\end{align*}
\]

\[
\begin{align*}
\text{Mean DDFTV/cm}^3 & \text{(Study 2)} \\
\text{Day} & \text{2} & \text{4} \\
\text{Con HeN} & 0.35 \pm 0.086 & 0.39 \pm 0.051 \\
\text{Lpt HeN} & *0.63 \pm 0.022 & *0.76 \pm 0.025 \\
\text{Lpy HeN} & *0.45 \pm 0.039 & *0.46 \pm 0.035 \\
\text{Con HeJ} & 0.34 \pm 0.016 & 0.36 \pm 0.032 \\
\text{Lpt HeJ} & *0.40 \pm 0.026 & 0.51 \pm 0.028 \\
\text{Lpy HeJ} & 0.31 \pm 0.014 & 0.40 \pm 0.058 \\
\end{align*}
\]

185. Prognostic value of ploidy and proliferation markers in renal cell carcinoma

A. Tanapfe1, H. Hahn1, A. Katzin1, R. Fieberg1, A. Kühn1, Ch. Wittekind1
Department of Surgical Pathology1, Medical Statistics2, Radiosurgery1 and Urology1, University of Erlangen-Nürnberg, Germany

The prognosis of patients with renal cell carcinoma depends mainly on the pathological stage and grade of the tumour at time of operation. Cellular proliferation may prove to be another measure of predicting the biologic aggressiveness and therefore the prognosis. The AgNOR (Nuclear Organizer) is a component of the nuclear matrix which is involved in the control of cell proliferation. The number of AgNOR dots in variable proportions. Statistical correlations were seen between tumour grade, the rate of nuclear positivity for MIB-I and PCNA and survival rate and finally, we assessed whether the methods led to similar results.

In each carcinoma examined, we could demonstrate MIB-I, PCNA and AgNOR dots in variable proportions. Statistical correlations were seen between tumour grade, the rate of nuclear positivity for MIB-I and PCNA and the number of AgNOR dots. Additionally, the MIB-I-index was significantly higher in more advanced tumour stages. A good correlation between MIB-I and AgNOR and also for PCNA was found. In univariate survival analysis stage and grade, MIB-I and PCNA index and mean AgNOR-number were significant factors influencing patient's survival.

Performing Cox multivariate disease related survival analysis, stage of disease and MIB-I were the two significant independent prognostic factors. Flow cytometry was neither related to patients' prognosis nor to other parameters examined.

These results indicate that MIB-I immunostaining is an additional prognostic parameter which could provide auxiliary information for patients' survival rate and finally, we assessed whether the methods led to similar results.
outcome. MIB-1 and PCNA immunostaining as well as AgNOR showed a good correlation with each other. We failed to establish flow cytometry as a method for predicting proliferative capacity of prognosis in renal cell carcinoma.

186. Modified Indiana pouch following pelvic exenteration: urodynamic results in 20 patients

F. Blidou, G. Hoveneugebel, G. Serment, G. Gutelis, J. R. Delpepo
Marseille, France (Presentation by Dr. Blidou) Institut Pauli-Cabannes, 222 Rue Sainte Marguerie, Marseille Cedex 9, France

Introduction and objectives: Quality of life improvement is a goal after curative pelvic exenteration performed in young women with advanced gynaecological malignancy. In these cases, pelvic reconstruction including colorectal anastomosis, vaginal replacement, and continent urinary diversion performed. We chose the modified Indiana pouch procedure using automatic suture devices with absorbable staples to make the right colonic reservoir for a simpler and less time-consuming form of continent urinary diversion. Methods: Urodynamic studies were analyzed from a series of 20 patients who underwent pelvic exenteration with modified Indiana pouch since January 1993, with a mean follow-up of 13.6 months (range: 6–32). Urodynamic studies were performed at 6, 12 months and once a year.

Results: The average colorectal pouch baseline pressure was 9.4, 7.6, and 6.5 cm H2O, and the average maximal pouch capacity was 433, 535, and 632 cm H2O at 6, 12, and 24 months respectively. The basal pressure in the reservoir rose progressively as filling increased. In 3 patients (15%), residual reservoir contractions were noted (mean contraction pressure: 32.5 cm H2O) with occasional urine leak in 1 case. In these 3 patients, reservoir contractions decreased after oral administration of prifinium. The mean pressure was 61 cm H2O in the tapered ileum and 75.5 cm H2O in the ileocecal valve. Overday continence was satisfactory for all patients, with occasional urine leaks in 3 patients treated successfully with prifinium in 1 case of reservoir contractions, and by increasing the catheterization frequency in the other 2 cases.

Conclusions: The modified Indiana pouch is a simple and reliable urinary continent diversion, allowing a better quality of life in patients after pelvic exenteration. Urodynamic studies are important to detect and to treat subclinical abnormalities, such as reservoir contractions, pouch baseline high pressure, or low pressure in the efferent limb.

Gynaecology

187. Rectosigmoid resection in ovarian cancer—end colostomy vs reanastomosis

N. C. Gleson, M. S. Hoffman, J. V. Fiorica, W. S. Roberts, D. Cavanagh
The University of South Florida

This is a comparative study of our experience with end colostomy and rectosigmoid reanastomosis when colorectal resection was performed as part of the primary or secondary cytoreductive effort in epithelial ovarian cancer (EOC). The clinical and histopathological data of all patients with EOC undergoing rectosigmoid resection during a six and a half year period were reviewed. Fifty-four rectosigmoid resections were performed as part of the primary (n = 27) and secondary (n = 27) cytoreductive effort. No patient had complete bowel obstruction preoperatively. Operating times, peroperative and immediate postoperative morbidity rates were similar in the two groups. There was one postoperative death related to septicemia. Five patients with reanastomosis and six with end colostomies developed proximal bowel obstructions. Three (15%) patients developed serious complications (recto-vaginal fistula (n = 1), rectal stricture (n = 2)) in relation to their reanastomosis. Sixty-five percent of patients with rectosigmoid reanastomosis achieved normal long-term colorectal function. When technically feasible colorectal reanastomosis is worthwhile in EOC patients requiring rectosigmoid resection.

188. Second-look laparotomy in advanced ovarian cancer

M. Katsoulis, G. Vorgias, J. Panagiotides, C. Farafelos, B. Dertimas, J. Zis
Department of Gynaecology, Metsovo's Cancer Hospital, Piraeus

The value of prognostic parameters in predicting the outcome of second look laparotomies (SLL) and survival after SLL was assessed in a series of 115 FIGO III and IV ovarian cancer patients. The prognostic parameters included age of patients, FIGO stage, differentiation of tumour, maximum diameter of residual disease following the initial operation and clinical, cytologic and histologic results of SLL. No statistically significant difference was found between stage III and IV patients concerning the results of SLL (P < 0.09) and the same is true for the tumour differentiation (P = 0.41) and the age of the patient when first operated (P = 0.15). On the contrary, residual disease following the initial operation is shown to be prognostically significant (P = 0.001). As for the overall survival time, the amount of residual tumour after the SLL is shown to be the most important parameter (P = 0.0002).

Thoracic

189. The role of bronchoscopy in detection of tuberculosis and lung cancer

R. Jakovic, M. Prekajski, T. Radosavljevic, V. Cemenkic
Center for Thoracic Surgery, Clinical Center of Serbia, Beograd, Yugoslavia.

Introduction: The risk of lung cancer has been reported to be increased among people with a history of tuberculosis (TBC). The locations of the granulomatous fibrotic lesions are highly correlated with that of the lung cancer and is higher for adenocarcinoma than for squamous or oat cell carcinoma.

Materials and methods: The analysis was retrograde and included the patients surgically treated for bronchial carcinoma during a two year period (1994–1995). Out of 761 patients operated on for lung carcinoma 64 (8.4%) were selected since their operated specimens confirmed lung cancer and tuberculosis. In none of studied patients had active lung TBC been suspected. All patients were smokers. Bronchoscopes findings were directed towards signs of endobronchial Tbc or its effects and to confirm lung cancer and Tbc.

Results: Bronchoscopy revealed endoscopic tumour signs in absence of Tbc in 16 (25%) patients, indirect tumour signs and absence of Tbc in 10 (15.6%), normal findings in 13 (20.3%). The scars with anthracosis together with a visible tumour 3 (3.1%) secretion and/or inflammation in absence of tumour 9 (14.1%). TBC infection was preoperatively diagnosed in 4 (6.3%) patients only although none of them had suspected disease. Lung carcinoma was preoperatively confirmed in 46 (71.9%)—direct biopsy of tumour 18 (28.1%) small forceps biopsy of peripheral lesions in 12 (18.4%) transbronchial needle biopsy in 4 (6.3%). Adenocarcinoma was at the scar in 57.14% and epidermoid carcinoma in 38.1%. Old fibrotic lesions coexisting with lung cancer were epidermoid carcinoma 81.25% and adenocarcinoma 9.37%.

Conclusion: Adenocarcinoma is the predominant tumour at the site of fibrotic scar. Bronchoscopy can help in the diagnosis of active lung tuberculosis in cases with no clinical signs of disease.

190. Resection of non small cell lung cancer involving the thoracic wall

M. Mazzetti, F. Fusagalli, R. Cappelli, T. Panigalli, D. Peta
Department of Thoracic Surgery, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy

Lung cancer involves the chest wall with its direct invasion in approximately 2-8% of the patients. In these cases the prognosis seems to depend directly...
on lymph nodes status (N) better than local extension of the neoplasm (T), so that in the most favourable cases (T3N0M0) the 5-year survival rate is better than the remaining stage IIIA patients.

Between 1976 and 1989, 1365 patients underwent resection of non small cell lung cancer (NSCLC) at the General and Thoracic Surgery Department of University of Milan. This paper is concerned with 73 of these patients (5.5%) in whom the chest wall resection (ranging from 1 to 3 ribs or part of the sternum) for direct tumour invasion (T3) was required. The reconstruction of the thoracic wall was performed with direct closure of the parietal defect or using rib mobilization, dura mater, Marlex mesh and muscle flaps depending on the amount of chest wall excised. The resection of the chest wall was performed combined with pneumonectomy in 3 patients, with lobectomy in 61, with segmentectomy in 2 and with wedge resection in 7 cases. 41 of these 73 patients (56%) had negative lymph nodes, 21 (28.5%) had positive N1 lymph nodes and 11 had mediastinal N2 positive nodes. The overall 5-year survival rate is 31.5% (23 patients); 17 (74%) were N0, 5 (21.7%) were N1 and only 1 (4.3%) was N2.

In conclusion our experience confirms earliest reports: stage IIIA patients with chest wall involvement but without lymph nodes metastases (T3N0M0) have a better 5-year survival rate than N1 and N2, resulting a potentially radical excision of the tumour even in this advanced stage.

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**Abstracts**

### Sarcoma/Bone

191. Importance of early extratumoral surgery on outcome of localized Ewing sarcoma of pelvic bone

G. Delapine, N. Delapine, H. Cornille, S. Alkallaf, B. Markowska, J. C. Dupons

Oncologic Paediatric service, Hôpital R. Dubrè, 48 Bd Serrurier, 75019 Paris

**Introduction:** Local treatment of Ewing’s sarcoma is difficult and controversial. High dose radiotherapy is followed by 20 to 40% local recurrence and surviving patients are threatened by secondary sarcoma. Surgery is a challenge to evaluate the role of surgery and its modalities on outcome we reviewed our file.

**Material:** From 1968 to 1995, twenty one patients (15 boys and 6 girls aged 12 to 35 years) have been treated by authors for Ewing’s sarcoma, P.N.E.T. of innominate bone. 6 of them were primary metastatic to lungs and or bone.

**Patients:** All patients received polychemotherapy according to protocol and local treatment consisted of radiotherapy alone (5 cases), surgery and radiotherapy (10), surgery alone (6 cases). Surgery was then done in 16 cases (extratumor) in 9, contaminated in 7) either early, (before the 60th day of biopsy) or late. All patients had limb salvage with no reconstruction (2 cases) or reconstructive procedure adapted to anatomic site of tumour. In extra acetabular tumour, we used composite reconstruction with acrylic cement and screws or allograft (9). For periarticular lesions, we used combined total hip prosthesis (5).

**Result:** With a median follow up of 66 months, we have seen 6 (25%) local recurrence (all followed by metastases) and 8 primary metastatic evolution.

Only 7 patients (33%) are alive and well.

Statistical analysis confirms the worse prognosis for big tumours and bad response to induction chemotherapy. It also shows, for primary localised tumour the crucial importance of early extratumoral surgery. All 7 patients treated with radiation therapy alone or debulking surgery followed by radiotherapy subsequently died, without local control in 5.

Among the 8 patients treated by extratumoral surgery, the prognosis depends on early resection. 5 out of 6 patients with early extratumoral surgery are alive and well but 2 of those with late surgery relapsed.

Conclusion: Surgery increases the disease free survival rate of patients with Ewing’s sarcoma of pelvis. The lesion must be widely excised i.e. the resection must be extratumoral. Early removal of tumour volume is critically important and enhances the value of chemotherapy.

192. Trans-pediculer biopsy of vertebral body lesions

J. Bée and S. K. O’Bourke

St Vincent’s Hospital, Elm Park, Dublin 4, Ireland

The pathological significance of lesions in the vertebral bodies detected by imaging techniques presents a diagnostic and management problem for the clinician.

Aims: The aim of this study is to present our experience of performing biopsy of radiologically detected lesions in vertebral bodies using the transpediculer route.

**Population studied:** A population of 17 consecutive patients who underwent percutaneous transpediculer biopsy of lesions in the vertebral body was studied. Each patient had suspected malignant disease and required tissue diagnosis for further management. The patients clinical records were reviewed and all patients with negative histology were followed up at a mean of 2.5 years after the biopsy.

**Results:** The vertebral biopsied ranged from T2 to S1. In 8 cases a positive diagnosis of malignant disease was made and in 9 cases a clinical suspicion of neoplasia was successfully ruled out. One patient required rebiopsy but no other complication resulted from this biopsy technique.

Conclusion: Percutaneous transpediculer biopsy of the vertebral body is a minimally invasive technique which enables accurate tissue diagnosis of suspicious lesions in the vertebral body.

193. Soft tissue sarcomas of the extremities: a retrospective study of 85 cases


Instituto Português de Oncologia Francisco Gentil Centro Do Porto, Rua Dr. António Bernardino de Almeida, 4200 Porto, Portugal

The authors retrospectively studied 85 patients with soft tissue sarcomas of the extremities treated consecutively in the Surgical and Medical Oncology Departments of the Portuguese Institute of Oncology of Oporto, between January 1985 and December 1994.

Our main goal was to assess the results of the instituted treatment with special attention to the prognostic factors. In our group of 85 patients, 39 (46%) were males and 46 (54%) were females. Their mean age was 51.8 years, being 58.8% of our patients older than 50 years of age. The most frequent clinical presentation was the perception of a tumour, present in 92% of the cases. The mean interval between the appearance of the first sign or symptom and the diagnosis was 11 months.

In 25% of the cases the sarcoma was located in the upper extremity. Fifty-two per cent of the cases were localised in the lower extremity above and in the knee joint and 23% below the knee. The predominant histologic types were the following: Malignant Fibrous Histioscytoma (27%), Liposarcoma (21%) and Fibroscarcoma (12%). In terms of grading, 33% of the cases were high grade tumours and 55% were high grade lesions. The mean size of the tumours was 9.8cm with a minimum size of 2cm and a maximum size of 32cm.

Seventy-six patients were treated in a curative manner while 9 patients had palliative treatment. Of those 76 who were submitted to curative therapy, 14 were treated only with surgery, 20 with surgery and radiotherapy, 16 with surgery and chemotherapy and 26 with surgery plus radiotherapy and chemotherapy. We performed limb-sparing surgery in 65 cases and 11 amputations, none in the last 3 years of this study. The most frequently used chemotherapy regimens were Doxorubicin + DTIC (62%) and Cyvodic (29%).

The mean follow-up was 41.2 months with a minimum of 7 months and a maximum of 152 months. At 60 months of follow-up, the disease-free survival and the overall survival were 56% and 74%, respectively. In the group of patients submitted to curative therapy, the prognostic factors that showed a significant statistical relationship (P<0.05) related with disease-free and overall survivals were tumour grade (P=0.002 and P=0.01, respectively) and tumour size (P=0.02 and P<0.05, respectively).

The results obtained in this group of patients confirm the present concepts on the importance of grading and tumour size in the prognosis of soft tissue sarcomas of the extremities. We also stress the increasing frequency of limb-sparing surgery.
194. Utilization of CO2 100 W laser lancet in the surgery of malignant soft tissue tumours of the limbs

C. Bălănecu, S. Diaconescu
Central Medical Hospital, Bucharest Romania, Street Stefan Furthun 88, Clinic of Traumatology and Orthopaedics
In the period 1990–1995, in the Traumatology and Orthopaedic Clinic of the Bucharest Central Medical Hospital a CO2 100 W laser was used in 25 soft tissue sarcomas, as follows: dermatofibrosarcoma 2 cases, synoviosarcoma 4 cases, angiosarcoma 2 cases, liposarcoma 11 cases, fibrosarcoma 4 cases, leimyosarcoma 2 cases.
The age range of the patients was between 20 and 74 years and the tumour was in the lower limb in 20 patients. The patients were investigated by means of clinical and paraclinical examinations and also by means of other examinations such as scintigraphy, arteriography, echography, computerized tomography. Tumour staging was as follows: stage I 2 cases; stage II 20 cases; stage III 3 cases.
Depending on the T.N.M.G. staging, after incisional biopsy and cytostatic and radiotherapy treatment, we used: large excision—17 cases; radical excision—5 cases, followed by cytostatic therapy. The CO2 100 W laser lancet was used for: incisional biopsy (25 cases), ablation and vaporization of restant tumours (22 cases). In our group we had 5 recurrences with 3 deaths, in patients reviewed between 1 year.

195. Thermal preconditioning (thermotolerance) protects against leukocyte-endothelial interactions in-vivo

G. Chen, C. Kelly, K. Stokes, J. Wang, D. Boucher-Hayes
Royal College of Surgeons in Ireland, Department of Surgery, Beaumont Hospital, Dublin 9, Ireland
The clinical use of interleukin-2 (IL-2) has been limited by a leukocyte-mediated endothelial injury, known as the vascular leak syndrome (VLS). Leukocyte adherence and migration are critical events in the development of VLS. Exposure of cells to a sub-critical stress, such as hyperthermia (thermotolerance) may protect cells from subsequent injury, possibly by inducing heat shock protein (HSPs) expression. However, the role of thermotolerance in decreasing VLS is unknown. The present study investigated the effect of thermotolerance on leukocyte adherence and migration induced by IL-2 in rat mesenteric post-capillary venules (20–35 μm). Sprague-Dawley rats were randomized into IL-2 only and thermotolerance + IL-2 (T + IL-2) groups. Thermotolerance (elevating core body temperature to 41 ± 0.5°C for 15 min) was induced 18 hrs prior to IL-2 administration (1 × 10^6 IU/rat). The number (No) of adherent and migrated leukocytes, and their rolling velocity were measured by intravital microscopy at baseline (0), and 30, 60 min after IL-2 injection. HSP72 expression in lung, intestine, and mesentery was determined by Western Immunoblotting.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>No. Adherence (1/mm)</th>
<th>No. Migration (cells)</th>
<th>Rolling Velocity (μm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.7 ± 0.42</td>
<td>1.3 ± 0.33</td>
<td>1.5 ± 0.56</td>
</tr>
<tr>
<td>30</td>
<td>10.5 ± 2.04</td>
<td>1.8 ± 0.40</td>
<td>1.5 ± 0.34</td>
</tr>
<tr>
<td>60</td>
<td>18.2 ± 5.12</td>
<td>3.0 ± 0.37</td>
<td>1.6 ± 0.65</td>
</tr>
</tbody>
</table>

Data: Mean ± SE. Stat: Unpaired Students’ t-test, *P<0.05 IL-2 vs IL-2 + T; P<0.05 Vs 0 min.

In this model, IL-2 significantly increased leukocyte adherence and migration, and decreased leukocyte rolling velocity at 30 and 60 mins. Thermotolerance prevented IL-2-induced increases in leukocyte adherence and migration, and the decrease in leukocyte rolling velocity. This was associated with an increase in HSP72 expression in the lung, intestine, and mesentery compared with IL-2 alone. This study demonstrates that thermotolerance inhibits leukocyte-endothelial interactions possibly by increasing expression of HSP72 in tissues, suggesting a role for thermotolerance in treating leukocyte-mediated microvascular injury.

196. HSP70 causes protection to tumour cells following heat shock from monocyte mediated lysis

F. Campbell, H. P. Redmond, J. Harney, D. Boucher-Hayes
RCSI Dept. of Surgery, Beaumont Hospital, Dublin 9, Ireland
Introduction: It is well documented that, despite host production of tumouricidal mediators, tumour cells continue to proliferate. This could be due to induction of a protective stress gene response in the tumour cell. The aim of this study was to assess the effect of heat shock on tumour cell cytoplasmic stress gene activation and to correlate it to monocyte-mediated lysis.
Methods: SW707 cells, a human colorectal cell line, were subjected to a heat shock induced by either sodium arsenite (SA, 0-320 μM for 6h) or by hyperthermia (42°C, 30 min, followed by a 2h recovery period). Monocyte-mediated cell lysis cytotoxicity was assessed by labelling treated cells with 51Cr and incubating them with human monocytes isolated by density centrifugation from healthy volunteers. Whole cell lysates of treated cells were made and run on Western blot and probed for heat shock proteins (HSP). Untreated cells were fractionated and fractions run on WB and probed for HSP. To assess the toxicity of sodium arsenite, cells were grown on microscope plates in the presence of SA for 6h and the end point was assessed by crystal violet dye elution. Statistics were by ANOVA with Scheffe post hoc correction.

Results: The cytotoxicity results showed a significant decrease in all treated groups (P<0.00003) when compared to the control value of 40.45 ± 0.81%. The western blot data shows that following heat shock, HSP70 expression but not HSP27, HSP60 or HSP90 is increased indicating that HSP70 is the HSP responsible for the protective effect seen when SW707 cells were used as targets in monocyte-mediated lysis. HSP70 is found to reside mainly in the cytoplasm in untreated cells. Sodium arsenite is found not to be toxic to the cells at the doses and the time point in question.

Conclusion: This study shows that the resistance of tumour cells, following stress gene induction, to monocyte-mediated lysis correlates with an increase in cytoplasmic in HSP70. Attenuation of stress gene induction in tumour cells should increase susceptibility to monocyte-SA: sodium arsenite HSP: heat shock protein WB: western blot.

197. Generation of cytokine secreting tumour cell vaccines that inhibit the development of breast cancer metastases in tumour bearing mice

E. C. Cowen, R. M. Clary, M. Iacobucci, R. Philip, H. K. Lyerly
Department of Surgery, Duke University Medical Center, Durham, N.C., U.S.A.
The clinical application of cytokine gene therapy for cancer is limited by the difficulty in establishing cell lines from primary tumours for stable gene transfection. A novel gene delivery method was devised that produces transient transfection in primary human tumours. Experiments were performed to demonstrate its efficacy in generating tumour cell vaccines to inhibit metastases in tumour bearing hosts. Inoculation of 2.5 ×10^6 4T1 breast cancer cells into the footpads (i.e.) of Balb/c mice leads to local tumour growth and the development of pulmonary metastases. Interleukin-2 (IL-2) secreting 4T1 cells (4T1-pMP6A/IL-2) and control transduced 4T1 cells (4T1-pMP6A) were generated by lipofection using a cationic liposome complexed to a novel adenovirus-associated viral (AAV) plasmid encoding the IL-2 gene (pMP6A/IL-2). Unmodified 4T1 cells were inoculated i.e. on day 1. Weekly subcutaneous vaccination with PBS, 2 ×10^6 irradiated 4T1 cells or bulk transfected irradiated 4T1-pMP6A or 4T1-pMP6A/IL-2 cells was commenced on day 21. Hindlimb amputation was performed at a footpad diameter of 5-6 mm (mean 28 days). Mice were sacrificed 24 days postoperatively and metastatic disease was determined by weighing lungs at time of harvest.

A significant reduction was seen in the pulmonary metastatic load of mice immunized with cytokine gene modified tumour vaccine (4T1-pMP6A/IL2) when compared to mice given control vaccines (Kruskal-Wallis test, P = 0.0031) (*Mann-Whitney test).

These data provide preclinical evidence to support the use of bulk transfected gene modified tumour cell vaccines in patients with breast cancer.
444 Abstracts

198. Surgical decision-making for potentially malignant solitary pulmonary nodules is improved by 18-FDG positron emission tomography (PET)

P. A. Racmoni*, A. Vanderheft†, P. A. Greenjeo† and S. Goldman‡
Departments of Thoracic Surgery*, Radiology† and Nuclear Medicine‡, Hospital ERASME, Université Libre de Bruxelles, Brussels, Belgium

PET scan reveals an increased uptake of 18-Fluoro-deoxyglucose (FDG) by hypermetabolic tissues, mainly malignant. Between September 1995 and March 1996, 14 patients with pulmonary nodules less than 25 mm, without pathological diagnosis, have been evaluated by radiology and PET scan. Chest X-Rays and computed tomographies were non-contributory (1), benign (2), highly probably primary tumour (6) or possible metastases (5). High uptake of 18-FDG was detected in 10 patients. Thoracotomy was performed in 12 patients and 2 were carefully followed for probably benign nodules without FDG hyperfixation.

The impact of PET scan on surgical decision-making has been valuable: thoracotomy confirmed for 7 possibly malignant nodules, accelerated for 3 undefined nodules, postponed for 2 'cold' nodules, oriented to limited wedge resection in one central 'cold' nodule 20mm in size. FDG-Pet scan was non-contributory in a 5mm malignant carcinoid tumour revealed by Cushings syndrome and localized by NMR and octreotide uptake. There were no false positive evaluation of PET scan. One metastatic mediastinal lymph node had been detected. PET scan was poorly positive in discrete diffuse infiltrates of early bronchioloalveolar carcinoma.

The resolution of FDG-PET scan is related to the active tumour cell mass: in our serie. PET scan detects tumours of 10mm diameter (and probably less) in 65% cases. 1) to confirm or suggest malignancy; 2) to enhance the quality of the surgical decision and technical approach; 3) to reveal malignant deposits in areas with poor radiological definition.

199. Reconstructive surgery following oncologic resections: a virtual reality project

*Department of Plastic and Reconstructive Surgery, IST, University of Genova, Italy
**Department of Surgery, University of Genova, Italy
***Department of Communication, Computer, and System Sciences, University of Genova, Italy

Complex defects with extensive bone and soft-tissue loss of the facial region following trauma or ablative surgery usually require osteomyocutaneous flap transposition for restoration of natural maxillofacial contour. Unfortunately, operative assessment of the 'precise fit' of the flap, particularly regarding the size and the length of both the bone segment and the vascular pedicle, is perplexing as the surgeon reflects on nuances of geometry, shape, and contour. Starting from three 2-D MR and CT images of 256 x 256 pixels (each pixel represented by 12 bits), at the same slice location in a given patient, a new single image representation of all parameters has been generated by using the false-colour technique in a standard UNIX and X-11 environment. A transformation linking together the MR, CT parameters and the RGB (red, green, blue) colour components has been used. Each image of the various sequences is interactively displayed by using a specifically designed application based on a software layer named IAP (Image Application Platform, ISG Technologies, Toronto, Canada). The resulting images are displayed, using a resolutions of 24 bits per pixel, via an HP CRX24 graphic board, the stereo monitor allows the three-dimensional realism of visual data through LCD shuttered glasses (Crystal Eyes, Stereo Graphic Inc., USA). Moreover, a 3-D control system based on low frequency magnetic fields (Polhemus Fastrak) has been used, while a handheld Polhemus stylus can be used as an electronic knife for dissecting the 3-D data set. Thus we believe that our system, based on the HP9000/335 workstation (running UNIX X-11 OSF/MOTIF as graphic user interface), allows accurate 3-D pre-operative planning of various plastic reconstructive surgery procedures. Bone or soft-tissue contours can be analyzed, and sections can be removed from the model to allow a view of the underlying structures. In our hands, computer reconstruction of both donor and recipient areas, defined by computed tomography and magnetic resonance imaging, has allowed the representation of tissue-loss and flap volume in three-dimensional space. Flaps and grafts obtained utilizing the above-reported techniques can be fitted exactly, without repeated removal and recarving. Nuances of depth, tapering, and arc are carved directly into the bone, while chances of asymmetry are markedly diminished. In this way, aesthetic times are reduced by more efficient utilization of operative time, which usually offsets the increased cost of imaging.

200. Cefobid in prevention of postoperative PYO-inflammatory complications in oncologic patients

O. I. Ertshenkoo, D. V. Mysosylov
Kiev State Institute for Advanced Training of Physicians, Oncol. Dept., Kiev, Ukraine

Cefobid (Ceroperanzo)-cephalosporin antibiotic of the third generation with a wide spectrum of action was used for prevention of postoperative PYO-inflammatory complications in oncologic patients after surgical treatment. Bacteriological studies show that the most often excitors are colibacillus, Proteus vulgaris, enterobacter, pyocyanic bacillus and other Gram-negative microorganisms and their associations. The patients obtained radio- or chemotherapy.

Cefobid was infused intravenously 30-40 min before the operation in a dose of 1-2 g depending on the choice of operative technique; the subcutaneous nodule of cefobid -12 h. When infection was suspected in the area of operation infusion of cefobid lasted for 24-48 hours. 29 operated patients were under observation: 27 were operated for rectal and colon cancer; 2 - for gastric cancer. 24 radical operations were carried out. In the remainder of the patients during the postoperative period there were no any complications.

The preliminary results concerning cefobid use for prevention of postoperative PYO-inflammatory complications in oncologic patients indicate its efficacy and it can be recommended for wide use.

201. Clinical evaluation of a new centrally implanted port, accessed by catheter-over-needle systems

M. Pitsitucu, A. Astone*, M. Agresti, C. Barone*
Dept of Surgery and *Dept of Oncology, Catholic University, Rome, Italy

We have tested the 'Cath-Link 20' (CL-20, Bard, a new low profile venous port designed for access with a standard catheter-over-needle system. The CL-20 has many advantages, if compared to standard ports: (a) due to its small size, it can be implanted with minimal trauma to the subcutaneous pocket is created very easily, with a small skin incision; (b) the identification and cannulation of the CL-20 is easy and rapid: the port is accessed by a standard catheter-over-needle system (a 51 mm, 20 gauge 'Ivory', Beckton-Dickinson); (c) the access is reliable and comfortable for the patient: dislodgement of the catheter is impossible; (d) the external 20 gauge catheter is directly connected to the internal central venous catheter, and this allows a high flow system (up to 900ml/hr); (e) since the CL-20 has no reservoir and no septum, it can be accessed an unlimited number of times: if obstruction occurs, it can be easily managed passing a guide wire through the catheter. In previous reports, peripherally implanted CL-20 has proven to be associated with ease to access and low rate of complications (no extrusions; low incidence of infection and local complications; blood return always obtainable; nursing and patient acceptance was excellent. Since December 1995, we have inserted 10 CL-20, in 10 patients receiving chemotherapy for non-haematological neoplasms. All ports were implanted centrally, by internal jugular vein puncture, adopting the so-called 'low lateral approach'. Advantages of this approach are: (a) no risk of pneumothorax; (b) low incidence of accidental arterial puncture; (c) high rate of success at first attempt; (d) venipuncture is painless and the passage of dilator and introducer sheath is smooth and easy; (e) when the central venous catheter is inserted, an easy and relatively short subcutaneous tunnel leads it to the site of the port; also, there is no risk of the so called 'pinch-off syndrome, which occurs when the catheter is 'pinched' between the clavicle and the first rib. In all cases, the CL-20 was easily and rapidly implanted: there were no complications. All the CL-20 are still in use: they are accessed easily, with maximal patient comfort and no complications (in particular, we have had no obstructions and no infection episodes). A close follow-up is currently being carried out.

202. 52 cases of myasthenia gravis patients with thymomas

T. Otosu, K. Yagi, T. Yuri, Y. Imura and T. Matsumoto
Department of Thoracic Surgery, Fuchu Tokyo Metropolitan Hospital

We have operated 30 males (mean age 45.2) and 22 females (mean age 40.4) between July, 1973 and March 1996. The male cases were predominant. In thymomas, 19 cases was lymphocyte predominant type, 20 cases was mixed type and 13 cases was epithelial cell predominant type. Seven cases became worse rapidly after an observation period of over 2 years and were found to have tumour.
In treatments, we divided into 3 groups; steroid—operation—steroid sequence (group A), operation—steroid (group B) and operation only (group C).

Eleven cases were in group A and their clinical stages of tumour were over stage II (Masako's classification).

Two cases with epithelial cell predominance had recurrence. Twenty eight cases were in group B in which five cases had recurrence and all were stage III. Nineteen cases were in group C and no recurrence was seen in this group.

In stage I cases of either MG (osseomann) or thyroma (Masako), operation alone was required for cure.

203. Immunoprotected oncological surgery with interleukin-2 rationale and clinical results
F. Brivio, P. Lissio*, O. Brivio, L. Fumangali, M. Girlando, P. Gramazio, F. Uggeri
R. Surgical Clinic, Director F. Uggeri University of Milan, Monza Department San Gerardo Hospital Monza (Milan) Italy

Cytokines discovery rose new expectations for the immunologic therapy of tumours. After the first experiences with Interleukin-2 (IL-2), consisting pharmacologically active only for kidney carcinoma, this subject has been practically filed, perhaps leaving out the basically innovative cultural acknowledgement of this therapeutic approach.

In our opinion it is not possible to file the IL-2 subject without an appropriate experimentation on the fundamental goal to which this therapy is aimed: an essential change of the biological response to the tumour. As regards oncological surgery, this molecule in theory satisfies two important requirements: 1) to oppose the immunological deficits following surgical trauma and 2) to control a possible minimal remaining disease and malignant cell spreading that follows surgical handling. It is just with regard to these aims that is necessary to test such therapy in association with the surgical action.

Till 1990 by pursuing these premises we began to study on patients with colo-rec tal cancer and our goal was to verify the possibility to subvert post-surgical lymphocytopenia and to consider a probable interference with the prognosis of the disease. Theoretically in the immediate post-operative period, an activated lymphocytosis could have a basic part in controlling the neoplastic spreading during this delicate and weak period.

From July 1990 to December 1995 41 patients (M/F 26/14), median age 59 years (range 35-80), with colo-rec tal cancer (14 tumours operated with radical surgery—9 patients staged Dukes B, 3 Dukes C and 2 Dukes C-, 15 patients treated with palliative surgery and 12 relapses) had been treated with pre-operative IL-2 immunotherapy. The immunotherapy protocol provided 9,000,000 IU. IL-2 bid for three consecutive days, beginning since the fourth pre-operative day. We considered CD4, CD8, N.I., CD25 and CD3 lymphocyte subsets in the pre-operative period, in the 1st, 3rd and 7th post-operative day. The data had been compared with those of a group of 30 patients surgically operated in the same period but without immunotherapy. The biological results confirm the complete reversibility of the surgically-induced immunosuppression with a statistically significant difference of the lymphocyte count and the considered subsets. The preliminary clinical results showed that the patients treated with radical surgery (14 primitive tumours and 6 relapses) after a median follow-up period of 37 months (min 19 max 66) had a 25% relapses (5/20) vs 39% (13/34) of the surgically treated group but without immunotherapy of the same period. As this study wasn't a randomized one, this kind of results suggest interesting possibilities, but anyway worthy of a confirmation with appropriate studies. The median survival of the IL-2 treated patients who underwent palliative surgery (15 Dukes D and 6 relapses) was 14.8 g.e. 1.7 months vs 8.83 g.e. 1.1 months in the 23 control patients surgically treated but without immunotherapy (P = 0.01). Both groups received 5 F.U. and folic acid chemotherapy until progression of disease. If we can consider the improvement of the immunitary condition as a desirable goal to improve the surgical prognosis for oncological patients we believe that pre-operative IL-2 immunotherapy must be considered without any doubts. Our preliminary results confirm the treatment tolerability with a real immunitary activation that is evident with the post-operative lymphocyte subsets count. The preliminary clinical results, although not definitive, are worthy of confirmation with appropriate studies as for case histories and methods.

204. Splitting the pelvis to improve exposure in radical surgery for pelvic tumours in children
S. Adam, G. Bourke, R. J. Fitzgerald
R. J. Fitzgerald, Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland

Symphysiotomy was performed in the past to widen the maternal pelvis in difficult vaginal deliveries. It has also been used in reconstructive urological surgery. It's use in a total of three children for pelvic tumour excision has been reported to date.

We describe one patient who had public osteotomy and three who had sympotomies as an aid to radical tumour resections over the last seven years. In each it was possible to distract the pelvis so improving access to the tumour. All four patients had pelvic radioblastomas, three primarily the prostate and lower bladder and one a large tumour filling the pelvis probably of bladder origin. No immediate complications of the procedure occurred and no longer term ones in the two patients who died (two and a half years and one year post surgery) nor in the two survivors.

205. Surgical treatment of thyroma
C. Lequaglie, G. Giudice, M. Valente, G. Ravasi, G. Muscolino
Thoracic Surgery, National Cancer Institute of Milan, Italy

The aim of this study is to evaluate the impact of thyrometastases in patients with thymic neoplasms and to identify clinical and histopathological factors associated with improved long term outcome of surgery. We treated 79 patients with thymic disorders between February, 1987 and July, 1993. Thirty-seven were males and 42 females; the age ranged from 10 to 72 years.

Sixty-five patients were affected by myasthenia gravis. Before thyrometastases there were 4 patients with stage I disease according to Osgerman classification, 43 with stage IIa, 16 with stage IIb, and 2 patients with pharmacologic remission. There were 69 maximal thyrometastases by midstromectomy access. In the remaining 10 cases we performed an anterolateral thoraectomy. These last patients, all non-myasthenic, had benign thymoma but one had malignant disease. Minimum follow-up was 33 months. The specimen diagnosis was atrophic thymus in one case, no pathologic change in 33, hyperplastic in 10, benign thymoma (BT) in 28, malignant thymoma (MT) in 6, and non-specified thymoma (NOST) in the last case. About neoplastic disease there were 27 stage I (25 BTs, 1 MT, 1 NOST), 1 stage II BT, 6 Stage III (1 BT, 5 MTs) and 1 stage IV BT. The clinical status after thymectomy of the sixty-five myasthenic patients resulted in nine complete remissions (n=8), worsened (n=4), improved (n=13), much improved (n=20), pharmacologic remitted (n=3), and dead (n=4). Twenty-four patients with BT were alive without disease at the end of follow-up. 1 alive with a new tumour, 2 dead from disease recurrence, 1 dead from other disease: four patients with MT were alive without disease, 1 dead from MG without thymic disease progression and the last one dead from surgical complication; the patients with a NOST was alive without disease.

206. Urokinase plasminogen activator in basal cell carcinomas of skin
D. Chini*, T. Magisera, T. O'Reilly*, S. O'Sullivan*, N. O'Higgins*, M. J. Duffy†
Departments Plastic Surgery*, Surgery†, Nuclear Medicine*, St. Vincent's Hospital, Dublin 4, Department of Plastic Surgery*, St. James's Hospital, Dublin 8

Urokinase plasminogen activator (uPA) is a serine protease causally involved in cancer invasion and metastasis. In vivo, uPA acts by binding to a membrane-bound receptor, termed uPAR while its catalytic activity is controlled by its inhibitor, PAI-1. Basal cell carcinoma (BCC) of the skin is characterized by its low rates of formation of distant metastasis. This inability to give rise to regional or distant metastasis could be due to, either low levels of uPA or its low rates of formation of distant metastasis. This inability to give rise to regional or distant metastasis could be due to, either low levels of uPA or its low rates of formation of distant metastasis. This inability to give rise to regional or distant metastasis could be due to, either low levels of uPA or its low rates of formation of distant metastasis. This inability to give rise to regional or distant metastasis could be due to, either low levels of uPA or its low rates of formation of distant metastasis.

The aims of this study were therefore to assay uPA and its inhibitor PAI-1 in BCC and compare these levels to those of other skin cancers and invasive breast cancers. uPA, PAI-1 and uPAR were extracted from tumours tissue using 1% Triton X-100 in 50mM Tris-HCL buffer, pH 7.4 and then assayed by ELISA (American Diagnostica, 222 Railroad Ave, Grcenwieh, CT, USA). Mean values for uPA, PAI-I and uPAR in BCCs were 0.137±0.04 ng/ml. The proteolytic activity of PAI-1 in Squamous cell carcinomas (SCC) of the skin (median value 5.13±0.04ng/ml) were significantly higher than those in BCC (P=0.0074). While levels of both uPA and uPAR tended to be lower in BCC than SCC, differences were not statistically significant.

We conclude from this preliminary study that the failure of BCCs to metastasise is unlikely to be due to the presence of excessive levels of PAI-1. On the other hand whether decreased levels of uPA contributes to the low metastatic potential requires further study.
Completion thyroidectomy arises. In this retrospective study we reviewed an unselected series of patients in order to evaluate complication rates and loco-regional recurrences associated with total thyroidectomy (TT), completion thyroidectomy (CT) and partial thyroid resection (SR). The results of our study are presented as a decision tree generated by the Assistant-R machine learning algorithm. With this technique it has been found that the longest survival is predicted for patients without distant metastases, who are not in bad general condition and do not have a rapid tumour growth rate. In conclusion, the most important factors that predict survival are distant metastases and general condition of the patient: these are probably related to the aggressiveness of the tumour.

208. Completion thyroidectomy for differentiated carcinoma: when and why
P. Vitr, A. Galimberti, S. Piranlo and A. Bastagi
Surgical Department 'L. Sacco' Hospital, v. G. B. Grassi 74, 20157, Milano, Italy

Lobectomy + isthmectomy is the initial surgical treatment for thyroid nodules. Nevertheless pre- or intraoperative identification of carcinoma in a dominant thyroid nodule is occasionally difficult, due to well-known limitations or Fine Needle Aspiration cytology (FNA) and Frozen Section (FS) in follicular neoplasm. Furthermore, cancer can be detected in the thyroid extraglandular tissue surgically removed. The correct diagnosis becomes evident on permanent histologic section and the question of completion thyroidectomy arises. In this retrospective study we reviewed an unselected series of patients in order to evaluate complication rates and loco-regional recurrences associated with total thyroidectomy (TT), completion thyroidectomy (CT) and partial thyroid resection (SR).

Patients and methods: 76 patients with malignant thyroid tumours were observed and operated on at Surgery Department 'L. Sacco' Hospital, University of Milan between 1975 and 1995. The distribution of thyroid malignancies was: 64 differentiated cancers (46 papillary, 19 follicular), 3 medullary cancers, 3 primary thyroid lymphomas, 1 anaplastic cancer, 1 follicular-parafollicular carcinoma, 2 metastases (hepatocarcinoma, spinocellular). We considered 64 patients with differentiated cancer: there were 22 men (mean age 38 years, range 9-61) and 42 women (mean age 50 years, range 11-86). A dominant thyroid nodule was present in all patients and they were submitted to FNA preoperatively, in the last fifteen years, 18 patients were initially operated for clinical reasons, 25 patients for suspicious findings and 21 for malignant specimen. Intraoperatively, FS revealed a cancer in 15 previously classified benign or suspicious thyroid nodules. 16 suspicious nodules were classified cancer at permanent histologic sections. 37 patients were submitted to TT (group A), 27 to partial thyroid resection (9 subtotal thyroidectomies and 18 lobectomies); after results of permanent histology 15 patients were successively submitted to completion thyroidectomy (10 lobectomies and 5 subtotal thyroidectomies) (group B) and 12 patients (4 subtotal thyroidectomies and 8 lobectomies) (group C) were not reoperated. Reoperation for completion thyroidectomy was performed within three months. Follow-up ranges from 1 to 10 years (mean years). Patients were classified according to AMES score for risk factors: in the low risk group there were 39 patients (27 in group A and 12 in group C). In the high risk group there were 25 patients (10 in group A, 15 in group B and none in group C).

Results: 9037 patients (24%) in Group A and 515 patients (33%) in Group B were found to have cancer tissue in the controlateral lobe at permanent histology. Lymph node metastases were found during the first operation in 17 patients (46%) and a modified neck dissection was carried out. Lymph node metastases were found at completion thyroidectomy in 8 patients (20%). Surgical complications (laryngeal nerve palsy, hypocalcemia), loco-regional recurrences and mortality are summarized in the following table.

<table>
<thead>
<tr>
<th>Group</th>
<th>Hypocalcemia</th>
<th>Laryngeal palsy</th>
<th>P Recurrences</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>37 3.8%</td>
<td>3.8%</td>
<td>NS</td>
<td>3.8%</td>
</tr>
<tr>
<td>B</td>
<td>15 1.7%</td>
<td>1.7%</td>
<td>NS</td>
<td>1.7%</td>
</tr>
<tr>
<td>C</td>
<td>12 1.8%</td>
<td>0%</td>
<td>NS</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Mean free interval to recurrences was 39 months in group A, 62 months in group B and 36 months in group C.

Discussion and conclusions: It has long been recognized that well differentiated thyroid carcinomas have a relatively indolent clinical course, compared with other malignancies. Although the extraglandular extension and size of the primary tumour are associated with a poor prognosis, this is not demonstrated when multicentricity or lymph node metastases are present. The controversy is about surgical treatment of a tumour restricted to a single lobe and, in particular, the necessity to complete thyroidectomy when it is discovered at permanent specimens. Some authors consider extension of operation to a total thyroidectomy associated with an increased risk of complications and no advantage in loco-regional recurrence and survival. In our series, different rates in complications, loco-regional recurrences and mortality are not statistically significant between three groups of patients (TT, CT and ST). Completion thyroidectomy in patients with a cancer at permanent histology presumably confined to a single lobe is not related to a higher complication rate, but it seems unnecessary in patients with Low Risk AMES group. We suggest that completion thyroidectomy is necessary only in the High Risk AMES group patients.

209. Primary thyroid carcinoma of a thyroglossal duct cyst
R. Đukić, M. Josić, M. Kocić, M. Vlajčić, D. Trininić
Institute of Oncology and Radiology of Serbia, Belgrade, Yugoslavia

The thyroglossal duct cyst is the most frequent embryonal anomaly of the thyroid gland. In 1% of cases, thyroid cancer is found in this cist, most frequently papillary carcinoma. In the literature, 127 cases of the thyroglossal duct cyst carcinoma, surgical treatment is based on the individual experience. We diagnosed and treated two patients with thyroglossal duct cyst carcinoma during 15 years. Both patients were female, 27 and 51 years old at diagnosis. The younger patient had papillary carcinoma and lymph nodal metastases, while the other had follicular carcinoma in thyroglossal duct cyst and intrathyroid simultaneous follicular carcinoma. In addition to the excision of the thyroglossal duct cyst according to Sistrunk, both patients were treated with total thyroidectomy, dissection of submental and prethyroid lymph nodes. One of the patients had modified radical dissection of the lateral lymph nodes of the neck (MRND). Follow-up period of 10 years in one patient and 6 months for the other. We think that it is necessary to remove every thyroglossal duct cyst with excision (Sistrunk) and frozen section histopathology examination. If the diagnosis reveals a thyroid carcinoma, we recommend dissection of submental and prethyroid lymph nodes. At the same time, it is necessary to evaluate jugular lymph nodes at the level of carotid artery bifurcation (subdigastric), through the same incision. If they are metastatic, we recommend MRND during the same intervention. For patients younger than 45 years we suggest wide isthmectomy for frozen-section histopathology examination, and for patients older than 45 years—total thyroidectomy with frozen-section histopathology examination.
Abstracts

210. Total thyroidectomy for differentiated thyroid cancer

M Musella*, N. Iannare, A. Carrano, P. Castaldo, P. Giannasio**, S. Musella
Catanzaro Medical School, General Surgery, *Endocrine Surgery and **General Surgery Tinchio Hospital (MT) Italy

From March 1987 through March 1996, a total thyroidectomy (TT) has been performed on 258 patients treated in our center. Of them 39 TT have been performed on cancer patients (29 females, 10 male, mean age 66.5 ± 15) for papillary tumors, 9 for follicular carcinomas, 9 for mixed papillary-follicular carcinomas, for an indifferminated cancer and 1 for a lymphoma. By total thyroidectomy we mean a total extracapsular intervention. The morbidity rate for this intervention group has been: 1 patient had a temporary recurrent nerve palsy, 2 patients had a transient hypocalcemia, while only one patient suffered from permanent hypocalcemia.

We support TT as the right approach in patients suffering from differentiated thyroid cancer for the following reasons:

i) In patients in whom a preoperative diagnosis of differentiated thyroid cancer has been clearly obtained, TT allows a good ontological radicality and avoids the need for a re-intervention to remove additional thyroid tissue.

ii) In trained hands TT gives a low rate of complications that in addition to the advantages above explained makes this surgical approach to be preferred to less invasive interventions.

211. Surgery of thyroid carcinoma in children and adolescents

M. Auerperg, N. Belic, A. Pelis, S. Berstnar, H. Molicar
Institute of Oncology (101), Ljubljana

Thyroid carcinoma in children is a rare disease, and therefore experience with it even in larger centers is limited and controversy still exists regarding appropriate treatment. This study evaluates surgical treatment, complications and survival of patients (pts) younger than 21 years with thyroid carcinoma. From 1972-96 there were 42 such pts (28 females and 14 males; median age 17.5 years) treated at the Institute of Oncology (IO) and in 17 pts elsewhere. Extracapsular lobectomy (EKL) with resection of the isthmus on the site of the tumour was considered as the minimal adequate procedure in unilateral papillary follicular carcinomas. Nodudectomy or subtotal resection on the tumour site, or biopsy of lymph nodes was considered inadequate, and 8 pts after such surgery were reoperated upon. Altogether, EKL was performed in 15, "near-total thyroidectomy" in 13 and total thyroidectomy (TT) in 14 pts. TT was performed in bilateral tumours or in medullary carcinoma. Functional dissection of lymph nodes was performed in 15 pts, in 4 of them bilaterally. In 3 pts permanent unilateral paralysis of the vocal cords, and in 542 transient hypoparathyroidism occurred. All pts received L-thyroxine after surgery. In 16 pts postoperative treatment with I131 was administered. Pulmonary metastases developed in 7/42 pts. Two pts died, 37 are alive, and 3 were lost to follow-up. The incidence of regional relapses was significantly higher (P<0.01) in pts after primary inadequate surgery (58 pts) in comparison with patients adequately operated upon (4/30).

212. Serum thyroglobulin in the preoperative evaluation of follicular thyroid tumours

M. Hocevar, M. Auerperg
Institute of Oncology, Ljubljana, Slovenia

At present there is no reliable diagnostic test for preoperative discrimination between benign and malignant follicular thyroid tumors. According to the literature there is no value as it can be increased in malignant as well as in benign thyroid diseases. It was proposed that there may exist a cut-off point in the preoperative Tg level beyond which there is a strong probability that the thyroid tumor at the Institute of Oncology in Ljubljana, Slovenia, during the period 1990-1993, serum Tg was measured preoperatively in addition to standard preoperative tests (fine-needle aspiration biopsy, ultrasonography, "q'c scanning, hormonal profile). Postoperatively, patients were classified into six groups according to the histological diagnosis: 1—follicular carcinoma, 2—follicular adenoma, 3—Hurthle cell carcinoma, 4—papillary carcinoma (follicular type), 5—papillary carcinoma (classic type), and 6—nodular goiter; serum Tg concentrations within individual groups were compared. Median concentration value of serum Tg in individual groups were as follows: 1—3000; 2—197.5; 3—227; 4—100; 5—56; 6—228, 5ng/mL. Statistical analysis indicated serum Tg levels in the groups with follicular carcinoma and Hurthle cell carcinoma differed from all other groups (P<0.01). On the basis of these results we suggest, that serum Tg measurement should be included in the preoperative work-up of patients with thyroid tumours.

213. Importance of paratracheal nodal dissection in head and neck cancer

C. Timon, D. Hollywood, M. Toner
Department of Oral Head and Neck Surgery, St James' Hospital, James' Street, Dublin 8

Introduction: Head and neck mucosal squamous cell carcinoma readily involves regional cervical nodes and its presence is the foremost prognostic factor for these malignancies. Although neck dissection is the gold standard in the treatment of cervical spread, this does not routinely include paratracheal dissection. The aim of this study was to see whether paratracheal dissection is warranted.

Material and method: Over a 16 month period all patients undergoing laryngectomy were paratracheal dissection on a prospective basis, as a separate operation. Of the 22 patients analysed, the average number of paratracheal nodes dissected was 12. Nine of 22 patients had histological paratracheal lymph node metastases. The majority were <1cm in diameter. Preoperative clinical assessment and CT scanning failed to identify this disease. Paratracheal dissection added little to the total operating time and was without complication. Four of nine patients have died or developed regional/metastatic disease in a short follow-up period (3-21 months).

<table>
<thead>
<tr>
<th>Primary tumour</th>
<th>Number patients</th>
<th>Paratracheal positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngeal</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Hypopharyngeal</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Cervical oesophagus</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Conclusion: Paratracheal dissection should be routine in the surgical management of advanced pharyngeal, laryngeal cervical oesophageal tumours.

214. Pre- and postoperative supportive nutritional therapy via percutaneous endoscopic gastrostomy for patients with pharyngo-laryngeal tumours

S. Dubecz, Gy. Bodoky*, L. Haranczy* Dept. of Surgery of National Institute of Oncology, Bérz Grammar 7-9, 1122 Budapest, Hungary

Percutaneous endoscopic gastrostomy (PEG) is a simple and established pre- and postoperative nutritional support in patients with tumours in the head-neck region. Nasogastric (NG) tubes are useful for short term supplementation. However patients needing support for more than 6 weeks may be better served with a more permanent tube. The indications for our procedure were the inability to swallow secondary to neurological impairment (13 patients), cranio-facial trauma (8) and pharyngo-laryngeal tumours (20). We reviewed the records of patients with pharyngo-laryngeal cancer, who had PEG pre- or intraoperatively. The median age of this group was 49 years. Complete endoscopic gastro-duodenscopy was performed prior to the PEG placement. For preoperative nutritional support the patients received intragastric solutions (30 cal/kg "day") on the following day after the PEG placement. We performed PEG 3 weeks before the operation, with local anaesthesia, without antibiotic prophylaxis, by 'push technique' and discharged the patient from the hospital the following day. The mean length of PEG feeding postoperatively was 47 days. For patients with obstruction of the oro-oesophageal canal, who were not candidates for upper endoscopy, PEG was not performed postoperatively. Instead of open gastroscopy or feeding per NG tube, the PEG procedure is recommended preoperatively immediately after the resection, but before the reconstruction procedure. Moderate subtotal oesophageal obstruction occurred in 3 patients and catherter obstruction occurred on 2 occasions. Severe cellullitis of the stoma site was managed by temporary removal of the tube, nasogastric suction and antibiotics. There was no procedure-related mortality. PEG is a safe, simple and effective alternative to NG feeding even in patients with multiple medical problems. If, owing to obstruction, it is not possible to perform upper endoscopy, we suggest using PEG postoperatively.
215. Quality control and assurance in the diagnostics and therapy of thyroid carcinomas

G. Lukacs, Gy. Balazs, F. Gyory
1st Department of Surgery, University Medical School, H-4012 Debrecen P.O. Box 27, Hungary

The basic precondition for efficient quality control is the full documentation of pre-, intra- and postoperative findings. This documentation assures the improvement of the therapeutic procedures. The data-base of the 1st Dept. of Surgery of the Univ. Med. School Debrecen contains the records of 513 thyroid cancer patients operated on in the course of forty years. Included are: the case histories, previous thyroid operations, time and type of the actual surgical intervention, the operating surgeon, as well as the detailed surgical and pathohistological diagnoses, the complications, if any, and the follow up data.

<table>
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<tbody>
<tr>
<td>Thyroid cancer</td>
<td>112</td>
<td>123</td>
<td>134</td>
<td>145</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>69</td>
<td>78</td>
<td>87</td>
<td>96</td>
</tr>
<tr>
<td>Thyroid adenoma</td>
<td>12</td>
<td>14</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Chronic lymphocytic hyperplasia</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Chronic lymphocytic adenoma</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Thyroid hyperplasia</td>
<td>20</td>
<td>22</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Thyroid adenoma</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Chronic inflammatory disease</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

216. Interstitial hyperthermia of liver metastases with a US-guided ND-YAG laser

A Cappelli, P. Piro, L. Pippin*, G. Tantini
Institute of Surgical Clinic, University of Siena, *Department of Infectious Disease, Italy

The liver is the most common site of metastatic disease and the prognosis is very poor. The median survival for patients with liver metastases is 4-12 months from time of diagnosis. Treatments options are limited and actually the surgical therapy represents the gold standard. Only about 5-10% of patients are suitable for surgical resection with resulting 5 years survival of 20-40% depending on the type and extent of the tumour. Interstitial laser photocoagulation (I.L.P.) has recently been developed using a minimally invasive technique of local tumour destruction. Tumour is destroyed by direct heating, using low power laser light energy delivered via thin optical fiber inserted under ultrasound guidance. Five patients with a total of 10 metastases were treated using a percutaneous technique for fiber insertion. The treatments were performed using a continuous wave Nd-YAG laser. The laser fiber was introduced by a 18 gauge needle inserted percutaneously under US control. The laser was preset so that at power of 2.5 watt for 500-1000 seconds or 1000-2000 Joule. The metastases of small diameter (<3cm) were treated in only one session positioning the fiber tip on the lesion centre. For the metastases of larger diameter the fiber tip was repositioned by withdrawing it 1.5cm and the treatment was repeated few for session. Heating of the tumour was visualised by real time US as an expanding and coalescing echogenic zone around the fiber tip. The treatment was well tolerated and the patients were discharged in 24 hours. Follow up contrast enhanced CT scan and needle biopsy were carried out at 2 weeks from treatment. CT scan was repeated every 6 months and US control every three months. I LP is a technique in its infancy. Further research is necessary to improve its efficiency. Early data analysis about ILP compares well with 1-2 years post-surgical survival rate.

217. Monoclonal antibody SPan-I in detecting pancreatic cancer

2nd Department of General Surgery, Regional Hospital of Bolzano, Bolzano, Italy

The antigenic determinant recognized by monoclonal antibody SPan-I is greatly elevated in sera of patients with exocrine pancreatic cancer but not in sera of normal individuals. A soluble form of SPan-I is shed into the blood of inflammatory disorders of the pancreas. Experimental studies demonstrate that in malignant tumours of stomach and colon the blood level of SPan-I correlates closely with disease progression. This suggests that SPan-I could be an important tumour marker clinically. As preliminary studies showed soluble SPan-I to be increased in the blood of patients with pancreatic cancer, we tried to answer the question whether SPan-I could be a useful tumour marker in exocrine pancreatic carcinoma.

Between October 1994 and September 1995 we determined the levels of SPan-I in sera of 30 patients with ductal carcinoma of the pancreas, 12 patients with chronic pancreatitis and 20 healthy controls. The test for SPan-I consisted of a SPan-I-RIabead research kit (Dinabot Co., Tokyo, Japan) with a cutoff level of 30 U/ml.

218. Transaxillary access to effect locoregional chemotherapy with hepatic artery infusion (HAI) for secondary or primary hepatic tumours

*Division of Onglogical Surgery, University of Turin **Institute of Radiology, University of Turin #Laboratory Baldi e Riberi, A.O.S. Giovanni Battista, Turin 1° Division of Oncology-S. Giovanni Antica Sede Hospital-Turin

One of the biggest obstacles to the use of HAI is that in cases of metachronous metastasis (the majority), regional chemotherapy is only possible after surgical intervention to isolate the gastroduodenal artery and to place the tip of the catheter of the port in the hepatic artery with consequent creation of a subcutaneous pocket containing the port and Infusaid system. Such surgical intervention is not well tolerated by the patient because of morbidity and a small but significant mortality rate. In addition to cases of thrombosis of the catheter, dislocation and infection, the catheter cannot be further used and is generally not replaceable. Based on preliminary work of Japanese doctors from the University of Chiba, who developed a catheter coated with heparin on slow release, accessed by left axillary artery, and using a subcutaneous port (done under local anaesthetic), we have conceived a system of introduction similar to theirs for the performance of HAI. It uses catheters already on the market for other uses (spinal ports) and optimises the maintenance of the catheters. The drug used is the FUDR coated with heparin on slow release, accessed by left axillary artery, and optimises the maintenance of the catheters. The drug used is the FUDR according to classic scheme (0.3 mg/kg/day for 14 days) with addition of levocarvoin and dexamethasone. We have implanted 10 catheters using this method in patients with hepatic metastases from colorectal tumour. They all function perfectly. The age range is from 59 to 67 years. The KPS is above 60% for all. We have had no complications derived from the method. Other than the port, the catheters, if chosen, can be connected to an Infusaid. The operation was done in day-surgery and no conversion to an ordinary recovery was necessary. In case of occlusion, malfunctioning, dislocation or infection of the catheter, it may be replaced thus permitting the constant efficiency of the HAI. Given the harmless nature of the method and the possibility of substitution we believe such a route of access should be followed also in

### Hepato-biliary

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mean Value (U/ml)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy control group</td>
<td>8.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>22.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>216.9</td>
<td>298.1</td>
</tr>
</tbody>
</table>

There is a significant difference in SPan-I blood plasma level between patients with chronic pancreatitis and patients with pancreatic carcinoma in comparison with the control group (P=0.001). Sensitivity and specificity of SPan-I for pancreatic cancer in this population are 60.2% and 65.0% respectively (64.8% and 52.5% for an established marker as CA 19.9). SPan-I can be another useful serum marker in detecting pancreatic cancer.
cases of synchronous metastases of the colo-rectal tumour or in other tumours such as primitive tumours of the liver as suggested by the Japanese Authors.

219. Prevalence of cholangiocarcinoma in primary sclerosing cholangitis and its relevance for timing of transplantation

B. Nashan, T. Tsch, H. J. Schlitt, W. Wagner, R. Pichlmayr
Klinik und Poliklinik für Gastroenterologie und Transplantation, Medizinische Hochschule Hannover, Germany

Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease associated in 10% to 30% with hepatobiliary malignancies which are in the majority of cases known prior to transplantation. Diagnosis of carcinomas in a PSC setting at an early stage is yet not achieved. In order to assess optimal timing for transplantation in patients with PSC we applied the Mayo PSC risk model to 57 patients transplanted between 1982 and 1995. Out of these patients 11 had a biliary malignancy which was incidental in 9. According to the Mayo model low (n=12), moderate (n=16) and high (n=29) risk groups of patients were formed.

Results: The actual patient survival at 1 and 7 years were 100%, 100% (low risk), 68.6%, 68.8% (moderate risk) and 54.6%, 46.8% (high risk) respectively. Patients with a malignancy had a 30% survival at one year, none survived 6 years. Local recurrence of the tumour was found in 3 patients, two of them with low tumour stages at the time of transplantation.

Conclusions: Outcome of liver transplantation in PSC patients is dependent on the risk, stage and the formation of malignancies. Patients who are referred early in their course of the disease to transplantation have excellent survival rates and a low risk of tumour formation. On the other hand even patients with low grade malignancies in a moderate risk group have poor results, indicating that early timing of transplantation in patients with PSC is favourable. According to these results regular scoring of patients is suggested and transplantation should be taken into consideration at scores above 4.

221. Hepatic artery catheter complications

J. C. Doughty, G. Keogh, H. Warner, T. G. Cooke, C. S. McArdo
University Department of Surgery, Glasgow Royal Infirmary

Regional chemotherapy is one method of treating colorectal liver metastases with a reported survival of 18 months. Complications do occur directly related to the catheters and we describe 35 catheter related complications which developed in 106 patients receiving regional chemotherapy for colorectal liver metastases, and the methods used to deal with the complications.

All catheters were inserted by one surgeon. There were 33 minor and 12 major complications. Seven minor complications were related to the port and 8 with the catheter blocking or leaking. Fistulation into a surrounding structure occurred in 6 patients and extra-hepatic bleeding in 7 patients and pancreatitis and gastric perforation in 2 patients. Severe sepsis occurred in 3 patients and chemical hepatitis and hepatic failure were the 2 remaining complications.

We conclude that during regional chemotherapy catheter related complications do occur, but provided they are recognised they can be readily dealt with. Clinicians treating patients with regional chemotherapy should have a low threshold for investigating vague or gastrointestinal symptoms.

222. Hepatic resection as treatment for liver metastases from non-colorectal nonneuroendocrine cancer—is it worthwhile?

G. C. Panini, R. Bertu, R. Gafa, L. Pissano, A. Liboni
Institute of General Surgery and Institute of Pathology, University of Ferrara, Ferrara, Italy

Surgical resection of hepatic metastases has been demonstrated to be potentially curative only for cancer originating in the colon or rectum and for metastases of neuroendocrine tumours of the GI tract. The reduction in morbidity and mortality in patients undergoing hepatic resection has led to re-evaluation of the possible role of hepatic resection also in the management of metastatic liver cancer from non-colorectal (NCR) nonneuroendocrine (NNE) origin. Although the applicability of hepatic resections in this field has not been yet well defined, we have investigated in an anecdotal personal review whether a resection treatment can improve curability or palliation of a metastatic NCR NNE cancer.

This review includes three patients with metachronous solitary metastases to the liver from breast cancer; two patients with a solitary metastasis from pancreatic cancer; three patients with a solitary metastasis from renal cancer, a cutaneous melanoma and a neuroblastoma, respectively. Eight hepatic resections were performed to relieve the metastatic tumour, in the absence of disseminated metastatic disease, one left lateral lobectomy, two right posterior hepatectomies, three segmental hepatectomies, two wedge biopsies.

In the surgical review, two patients with breast metastatic tumour and the patient with renal cancer have survived two years, free of recurrent disease; one patient with pancreatic cancer survived more than one year without recurrence in the liver, developing systemic disease within second year. No long-term survival was recorded among the four patients with metastatic melanoma, neuroblastoma, breast and pancreatic cancer. The surgical indications must be compared firstly to the natural history of the primary tumour, secondly to the stage and extent of the metastatic disease to the liver and thirdly to the potential cost/benefit ratio for the individual patient.

On the basis of these observations, it is reasonable to restrict hepatic resections to selected patients having metastatic disease confined to a solitary hepatic lesion, no disseminated disease, no systemic tumour spread is expected in the short-term. In our series, this approach seems to be suitable only for cancer of breast and renal origin.

223. Resectional surgical procedures for pancreatic cancer. Results in 84 cases

S. Comunale, L. Troiano, S. Napolitano, A. Blanco, A. Giambusone, P. Iudici, C. Gitana, A. Lenitelli, F. Lauria
Doctor Troiano Lorezo. General Department of Surgery, Hospital Vittorio Emanuele II, Gela (CL), Italy

Surgical resection for adenocarcinoma of the pancreas carry considerable morbidity and mortality and only rarely results in long term survival. Although resection is the only potentially curative treatment for pancreatic cancer, typically fewer than 10% of all patients have disease sufficiently localized for surgical extirpation. Debate continues on the proper selection of patient for such radical procedures. We review here our experience with pancreatic resection in the management of pancreatic malignancies.

Material and methods: Eighty-four patients underwent resection in our department during the years 1974-1996. Fifty-five patients underwent duodenopancreatectomy. Thirteen total pancreatectomy. Fourteen patients underwent vascular resection (7 duodenopancreatectomy, 6 total pancreatectomy and 1 distal pancreatectomy) and 8 pylorus preserving pancreatectoduodenectomy. In the last 6 years 17 patients underwent subtotal extended duodenopancreatectomy as procedure of choice. Histological examination showed 8 ductal adenocarcinomas and 3 acinar cell carcinomas.

Results and conclusions: The resection was considered radical in 72 patients (85.7%) and palliative in 12. Overall hospital mortality and morbidity were 14.3% and 42.6%. In the last 8 years hospital mortality decreased to 3% and resectability rate increased from 16.4% to 34.4%. Morbidity and mortality rates were 35% and 12.7% after duodenopancreatectomy, 38.4% and 7.7% after total pancreatectomy and 18.7% and 6.2% after distal pancreatectomy. Mortality and morbidity rates were 7.7% and 30% after vascular resection and the same rate was found in pylorus preserving pancreatectomy. After standard Whipple operation, morbidity and mortality rate were 40% and 18.4% versus 35% after extended subtotal duodenopancreatectomy. Five years survival rate was 14.5% and 3.8% after duodenopancreatectomy, 8% after total pancreatectomy and 20% after distal pancreatectomy. No statistical difference was found in survival rate after standard Whipple resection and extended subtotal duodenopancreatectomy. Vascular resection improved resectability from 16% to 34.4%, and no difference in survival was seen between vascular resection and other resected cases.

Survival in our patients was only significantly influenced by lymph node involvement, degree of tumour differentiation and radicality of resection.

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224. Significance of overexpression of p53 and proliferating cell nuclear antigen (PCNA) in small hepatocellular carcinoma (HCC) tissue as prognostic factors

First Department of Surgery, Hokkaido University School of Medicine, Sapporo 060 Japan

HCC is highly malignant and frequently recurs after curative resection. The mutant type of p53 is considered to play an important role in carcinogenesis of HCC, and is expressed in about one third of HCC in Japan. We conducted immunohistochemical staining of p53 in small size human hepatocellular carcinoma (HCC) to evaluate its role as a marker of the biological malignant potential and prognosis after hepatectomy. One hundred and twenty-four cases of HCC which were treated by hepatectomy were divided into three groups: group A: tumour size below 2cm in diameter (n=21), group B: tumour size more than 2cm and less than 5cm (n=62), group C: tumour size more than 5cm (n=41). Immunohistochemical studies on overexpression of p53 were carried out by pretreatment with microwave oven heating as antigen retrieval. The sections obtained from resected specimen of HCC were dewaxed in xylene and rehydrated in alcohol. After washing in phosphate-buffered saline, the sections were incubated overnight at 4°C with p53 monoclonal antibody (DO-7. DAKO, USA) at a dilution of 1:100. The sections were incubated with biotinylated antibody for 30 minutes, followed by avidin-biotin peroxidase complex for 30 minutes. The peroxidase reactions were demonstrated using diaminobenzidine. PCNA staining was also done by ABC method using monoclonal antibody (DAKO, PC-10). Nuclear DNA of HCC cells were measured by flow cytometry and calciified as diploid and aneuploid estimated by DNA index. Rate of positive p53 overexpression in group A, B, C were 9.5%, 25.8%, 29.3% respectively which was significantly lower in group A (P<0.05). This was significantly higher in the tumour with capsular invasion and portal vein invasion. Well-differentiated types of HCCs had no p53 overexpression. DNA analysis revealed higher frequency of diploid pattern in group A. PCNA stain positive cells were 28.8±22.9% in group A which was not significantly different from the other two groups. Three and 5 years disease free survival rate after hepatectomy in group A were 39.8%. 29.9%, 29.3% respectively and survival rates were 88.9%, 47.4% which were better than group C (P<0.001). The patients with aneuploid tumours and tumours with 40% or more cells positive of PCNA had a significant poorer prognosis. In conclusion, p53 overexpression in small HCC reflected malignant potential of HCC cells. Further, positivity of PCNA staining was useful for predicting prognosis.

225. Radical operation for gallbladder cancer

S. Camlibel, A. Eroglu
Department of Surgery, Ankara Oncology Hospital, Ankara, Turkey

Prognosis of gallbladder cancer is poor. Aggressive surgery in gallbladder cancer has remained controversial. The medical records of 35 patients with adenocarcinoma of the gallbladder treated from August 1990 to October 1995 at Ankara Oncology Hospital were reviewed to examine the influence of aggressive surgery on patient survival. All the patients were first diagnosed by microscopic examination of the gallbladder, which had been removed for presumed benign disease. Of 15 patients underwent second-look operation, 7 were treated with radical cholecystectomy including extended lymphadenectomy (dissection of the porta hepatis, hepatic artery, pre- and retroduodenopancreatic, and celiac axis lymph nodes) with segmentectomy IV, V, and VIII or wedge resection of the gallbladder of the liver. There was no operative mortality. Patients were stagrd by TNM classification. Survival rates were calculated using Kaplan-Meier method and compared with log-rank test. Patients with early stage had significantly better prognosis than patients with advanced disease (P<0.01). In patients with stage I and II the median time was 14 months after simple cholecystectomy, whereas patients underwent radical cholecystectomy are still alive with the mean follow-up of 27 months. The median survival time at advanced stage in patients underwent simple cholecystectomy and radical cholecystectomy was 46 months and 10 months, respectively. Accordingly, we recommend that radical operation is a safe treatment of choice in gallbladder cancer.

226. Pancreatoduodenectomy and stapling of the pancreatic remnant for cancer: Personal experience

G. Nami, A. Scotti, G. Rosso, C. Botta, G. Balduzzi, P. Demichelli, M. DalFava, E. Coppi
General Surgery Division, S. Andrea Hospital, Vercelli, Italy

Introduction: The surgical treatment of resectable periampullary cancer (head of the pancreas, distal common bile duct and ampulla of Vater) is still a controversal matter: pancreato-duodenectomy (Whipple's operation) or total pancreatectomy. The arguments in favour or against these procedures are the maintenance of endocrine and exocrine function, the avoidance of the pancreaticejenoestomosis, the operative mortality and morbidity, the oncological radicality as well as the long-term survival.

Patients, methods and results: From 1985 to 1995, 53 pancreato-duodenectomies were performed with the following kinds of management of the pancreatic stump: pancreaticejenoestomosis 11 cases (21%), with two dehiscence (18%) and reoperation; pancreatic stump closure and Neoprene injection in the pancreatic duct 13 cases (28%), with 8 cases (53%) of diabetes mellitus, the follow-up and 2 pancreatic fistulas (13%) which healed in a few weeks; pancreatic duct ligation in (1 case external drainage of the duct) and pancreatic remnant stapling with fibrin glue protection and peroperative injection in the pancreatic duct 15 cases (28%), with 8 cases (53%) of diabetes mellitus, the follow-up and 2 pancreatic fistulas (13%) which closed spontaneously. The operative mortality was 2 cases (3.8%), due to severe bronchopulmonary complications.

Conclusions: It appears that the last procedure could reach all the proposed objectives: the maintenance of endocrine function without the risk of pancreaticejenoestomosis, and the same oncological radicality and long-term survival. The very low perioperative mortality and the good quality of life, in spite of the small number of patients, justify the further use and evaluation of this technique.

227. Is androgen receptor in large hepatocellular carcinoma as a prognostic factor after hepatic resection?

D.-C. Yeh, C.-C. Wu, T.-J. Liu, and F.-K. Peng
Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan

Hepatocellular carcinoma (HCC) is more prevalent in males than in females. Androgen receptors (ARs) in HCCs were reported to be associated with long term survival after hepatic resection. ARs in the cytosol of large HCCs (maximum diameter larger than 5cm) were determined between 1991 and 1993. Sixteen patients did not have detectable amount of AR in tumour. Fifteen patients had detectable amounts of ARs in tumour, ranging from 1.70 to 40.93 fmol/mg protein. There were no significant differences in the immunohistological characteristics of the resected specimens between patients with AR-negative HCCs and those with AR-positive HCCs. One patient who died of respiratory failure after operation was excluded from survival analysis. The pathological characteristics of the resected specimens were also different between both groups. Until June 1995, the 3-year disease-free survival rates were 44.4% in the group of patients with AR-negative HCCs and 37.6% in patients with AR-positive HCCs (P=0.8510). We collected that androgen receptor may not predict the long term prognosis after resection of the large hepatocellular carcinoma.

228. Inoperable liver metastases from colorectal cancer treated by systemic or loco-regional chemotherapy

B. Massidda, M. T. Ionta, A. Nicolosi, A. Tarquini
Institute of Surgery and Clinical Oncology, 09100 Cagliari, Italy

Eighty six patients, 46 males, in age from 28 to 75 years, PS=0-2, with measurable or evaluable unresectable hepatic metastases from colon (53 patients) or rectal (33 patients) carcinoma were assigned to the systemic q or resective therapies (16 cases, 41 patients). Response was evaluated after 3 months. A CR was defined as the disappearance of all measurable lesions. Partial response was defined as a reduction of at least 50% in the sum of the product of the long diameter of all measurable lesions. The mean duration of responses was 6 (3-14) months in ARM A, 8 (3-20) in ARM B and 10 (3-38) in ARM C. Overall survival was 10 (3-14) months. 12.5 (3-36) in ARM A, 26% in B and 13.79% in C. The mean survival was 42.8% in ARM A, 26% in B and 13.79% in C. The mean duration of responses was 6 (3-14) months in ARM A, 8 (3-20) in ARM B and 10 (3-38) in ARM C. Overall survival was 10 (3-14) months. 12.5 (3-36) in ARM A, 26% in B and 13.79% in C. The mean survival was 42.8% in ARM A, 26% in B and 13.79% in C.
Abstracts

229. Gallbladder carcinoma and point mutations of the p53 tumour suppressor gene
Chemurgische Klinik, Virchow Klinikum (Humboldt University), Augustenburger Plz. 1, D-13353 Berlin

In gallbladder carcinoma, studies on the prime target of genetic alterations in human malignancies, the p53 tumour suppressor gene, were focused on its immunohistochemical detection. The only published report on p53 sequence analysis in gallbladder carcinoma originates from the Japanese literature, demonstrating a 31% incidence of p53 point mutations which were not related to clinical features of these patients. From November 1991 to October 1993, 7 patients suffering from gallbladder carcinoma underwent surgical resection. Cancerous and normal liver tissue was obtained immediately after surgery, snap-frozen in liquid nitrogen and stored at -80°C. DNA was prepared by proteinase-K digestion and underwent PCR amplification of a 1574bp fragment corresponding to the exons 5-8 of p53 gene. Sequencing was performed using the dye-sequencing-termination method. Missense mutations were detected in the cancerous tissue of 2 patients—one transition each on the codons 134 (Phe→Leu) and 146 (Tyr→Arg). Immunohistochemical p53 staining was positive in the latter patient only. Clinical and histopathological features were evenly distributed in the wild-type and the mutation group. Significant differences were not observed, though all patients in the wild-type group had suffered from gallstones compared to no such patient in the mutation group. This is the first report on sequence analysis and mutagenesis of the p53 gene in western gallbladder cancer and reflects results obtained in Japanese studies. While both mutations were transitions, a uniform pattern could not be observed. Missense mutations were not significantly associated with any clinical or pathological parameter. Assessment of the impact of p53 mutagenesis on gallbladder tumorigenesis requires evaluation in larger study.

230. Adjuvant hepatic arterial chemotherapy in patients after complete resection of liver metastases of colorectal cancer
R. Seiring, W. Paddberg, C. Kelm, K. Henneking
Department of Surgery, University of Gaeassummy Germany

Almost 50% of the patients with colorectal cancer present liver metastases. At the time of diagnosis of the tumour one third of these patients already have a synchronous metastatic involvement of the liver, the other two thirds develop metachronous hepatic metastases. A complete surgical resection of these metastases improves the survival time of the patients concerned. It was of further interest if patients with liver metastases undergoing surgical treatment could benefit from additional adjuvant hepatic arterial chemotherapy.

Patients: From January 1987 to December 1994 a complete resection of liver metastases was performed on 68 patients suffering from colorectal cancer at the Department of Surgery, University of Giessen, Germany. In 25 patients the metastases had developed synchronously. 54 patients were treated with an adjuvant hepatic arterial chemotherapy. The chemotherapeutic regimen consisted of six cycles and was administered once a month. In each cycle the patients got 15mg Mitomycin C once and 1000mg 5-Fluorouracil per day over 5 days.

Results: Median survival of patients with complete resection of liver metastases and adjuvant hepatic arterial chemotherapy was 25.5 months. 3-year survival occurred in 43%. Patients undergoing surgical treatment only had a median survival time of 19 months and a 3-year survival of 29%. A significant difference in median survival between these groups could not be found (P = 0.103). It was of further interest if the effectiveness of hepatic arterial chemotherapy was depending on the onset of metastatic liver involvement. 17 patients with synchronous metastatic liver disease underwent surgical treatment and adjuvant hepatic arterial chemotherapy. 5 patients were treated by complete resection of liver metastases only. Median survival after 26 months with adjuvant hepatic arterial chemotherapy in comparison to 11 months with surgical treatment only. The difference was not significant (P = 0.224). 43 patients had developed metachronous liver metastases. While 37 of them were treated with complete resection of liver metastases and adjuvant hepatic arterial chemotherapy, 6 patients underwent surgical treatment only. Median survival time of those patients treated with adjuvant hepatic arterial chemotherapy was 25 months compared with 26.3 months of those undergoing surgical treatment only. A significant difference in median survival between these groups could not be detected (P = 0.224).

There is no statistical proof of the effectiveness of adjuvant hepatic arterial chemotherapy with Mitomycin C and 5-Fluorouracil on the median survival of patients after complete resection of liver metastases of colorectal cancer. Nevertheless further research seems to be promising.

231. Favourable prognosis of mucinous cystadenocarcinoma over ductal adenocarcinoma of the pancreas after curative resection
G. J. Ridder, H. Bechstein, H. Maschek*, J. Klempnauer
Clinic for Abdominal and Transplantation Surgery, Hannover Medical School, Hannover, Germany; *Department of Pathology, Hannover Medical School, Hannover, Germany

This report details 9 patients after curative surgical resection of histologically proven mucinous cystadenocarcinoma of the pancreas and compares the prognosis with ductal adenocarcinomas. The TNM classification of the UICC does not differentiate between adenocarcinomas and cystadenocarcinomas. Cystadenocarcinomas represented 2.1% (10466) amongst a total of 466 patients who underwent surgical exploration and 5.5% of all curatively resected carcinomas of the exocrine pancreas at Hannover Medical School from 1971 to 1994. 46% of adenocarcinomas and 90% of cystadenocarcinomas were resectable. A curative R0 resection was possible in all patients with cystadenocarcinoma and 85% with adenocarcinomas. Six of the patients with cystadenocarcinoma were female and 3 were male. Their median age was 54±12 years (range 44 to 81 years). Four cystic neoplasms were located in the head, 1 in the head and body, 3 in the tail, and 1 in the body and tail of the pancreas. There was no hospital mortality in this group.

The prognosis after resection of cystadenocarcinomas was significantly better compared to ductal adenocarcinomas of the pancreas. The Kaplan-Meier analysis revealed a median overall survival of 9 years versus 5 years, and a median progression free survival of 2 years versus 1 year. A univariate Cox regression analysis after curative resection of adenocarcinomas revealed only tumour size as parameter of independent prognostic value. Lymph node metastasis, distant metastasis, UICC-stage, and grading were of no additional prognostic significance. While the small number of only 9 patients with curatively resected cystadenocarcinoma a regression analysis was not possible. The descriptive analysis of the data, however, revealed that advanced tumour size and lymph node metastasis adversely affected long-term prognosis. Stage I cystadenocarcinomas did not recur and all patients survived beyond 5 years. Cystadenocarcinomas revealed a higher degree of differentiation. Even the patient with resected synchronous liver metastases survived more than one year. Our results indicate the favourable prognosis of mucinous cystadenocarcinoma over ductal adenocarcinomas of the pancreas in a cohort of patients with curative tumour resection.

Melanoma

232. Technique and results of therapeutic hyperthermic isolated limb perfusion (HILP) for the treatment of malignant melanoma
Th. Meyer, J. Göld, Ch. Haas, A. Altendorf-Hofmann, W. Hohenberger
Dept. of Surgery, University Hospital Erlangen-Nuremberg, FRG

HILP is a treatment modality that combines hyperthermia with the application of high doses of cytostatics after isolation of the extremity circulation. Multiple locoregional intransit metastases of malignant melanoma are a widely accepted indication for HILP.

From 1975 to 1994 a total of 131 patients were treated with HILP in a therapeutic setting, i.e. because of manifest locoregional metastases of melanoma localized to the extremities. The cytostatic used was melphalan; dacarbazine (1mg) was often applied in addition. During this period the perfusions were performed with tissue temperatures from 40.0°C-41.5°C over at least 60 minutes. Simultaneously, regional lymph node dissection...
was carried out. The best results were achieved in patients with satellites or intransit metastases exclusively (n=50) with 5- and 10-year sr of 60% (stage IIA according to M. D. Anderson classification). In case of simultaneous (n=32) or exclusive (n=48) regional lymph node metastases (stage IIB, IVA, and IVB), prognosis significantly deteriorated: the 5- and 10-year sr were 35% and 25% as well as 30% and 20% respectively.

Since 1992 a further group of 18 patients were treated with a modified perfusion technique. On the basis of experimental data, perfusion time was prolonged to 90 minutes and the drug was continuously infused over 20 minutes. Our experiences show an increase of remission rate that virtually does not distinguish from the results of TNF alpha-containing perfusion regimens, but for a final conclusion a longer time for follow-up is needed.

233. A new perspective in the treatment of nodal metastases for melanoma: sentinel node biopsy and selective dissection
F. Belli, L. Mascheroni, C. Clemente, L. Lenisa and N. Cescinelli
National Cancer Institute, Milan, Italy
The technique of sentinel node (S.N.) biopsy is a procedure allowing identification of the first node in the regional nodal area into which a primary melanoma drains. By this technique we could distinguish patients with clinically occult nodal disease from those whose lymph nodes are cancer-free. At the National Cancer Institute of Milano from February 1994 to February 1995, 55 patients affected with melanoma of trunk or limbs were submitted to intraoperative mapping for S.N. identification. No patient presented at the time of biopsy with a palpable node suspected for spread of disease. Intraoperative detection of S.N. was performed only by intradermal perilesional injection of 1-1.5 mL of Patent Blue-V about 20 minutes before starting nodal biopsy. In the majority of patients (94%) of this group only one stained S.N. was detected in each patient. Only in 4 cases (8%) two S.N. were identified. Nodal metastases were detected in 10 patients (20%). Detection by an intraoperative frozen section exam was obtained in 5 cases (50%). The incidence of positive S.N. correlated with depth of infiltration of primary: 1 positive S.N. for thickness between 1 and 1.99 mm, 2 for melanomas between 2 and 3.0 mm and 7 for lesions thicker than 3 mm. No distant metastases have been identified and all the patients of this group are alive and free of disease with a follow-up ranging from 1 to 24 months after S.N. biopsy. Our study indicates that occult localisation can be detected by S.N. technique and that such an approach could reduce the number of unnecessary lymphadenectomies introducing the concept of selective dissection as an alternative to 'elective' or 'delayed' dissection.

234. Sentinel lymph node biopsy in clinical stage IIA melanoma patients: our experience
A. Peressini*, C. Di Somma, M. Gipponi, M. L. Rainero, F. Filippi, C. Ferrari, P. Queirolo, M. R. Sertoli*, F. Cafiero*
National Institute for Cancer Research (IST) of Genoa; Dept. of Experimental and Clinical Oncology, University of Genoa, Italy
Introduction: The lymphatic mapping technique, performed by an intradermal injection of a vital blue dye adjacent to the melanoma is an useful approach to identify the occult lymph nodal metastasis in stage IIA melanoma, thus concentrating in these patients the potential benefit of an elective lymph node dissection.

Methods: In our experience sentinel lymph node biopsy has been performed in 34 patients with clinical stage IIA melanoma (pT3N0M0). Their mean age was 46 yrs (range 21-76 years) and their mean thickness 2.8 mm (>1 mm). The primary lesion was located in the trunk in four patients, upper extremity in 16 and lower extremity in 14.

Results: Sentinel node identification was achieved in the axilla in 75% of cases (15/20) and in the groin in 92.8% of cases (13/14). Additional sentinel nodes (blue stained) were found in eight patients (23.5%). Eight patients were found to have melanoma within their sentinel node on frozen section. Permanent sections stained by hematoxylin-eosin and immunohistochemistry has not found any additional patients with metastatic melanoma not identified by frozen examination.

Conclusion: Our experience with the sentinel lymph-node biopsy with the use of the dye alone confirmed that this technique has the potential to select patients most likely to benefit from elective lymph node dissection (ELND).