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ABSTRACTS

56th Scientific Meeting of the British Association of Surgical Oncology held at Liverpool Football Club on 25–26 June 1998

Abstracts of members' papers

Plenary session

Epithelial cell insulin-like growth factor type 1 receptor upregulation is an early event in colorectal tumorigenesis

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This study was designed to examine the role of the insulin-like growth factor type 1 receptor in human colon carcinogenesis. IGF-1 receptor expression was determined at the protein and mRNA levels in tumoral tissue and this compared to adjacent normal mucosa. Immunocytochemistry has shown upregulation of cytoplasmic-membrane IGF-1R expression in aberrant crypts (5/5), adenomatous polyps (34/34) and adenocarcinomas (24/27) in comparison to adjacent normal epithelial cells for all specimens. The immunolocalization of IGF-1R was especially pronounced in the tumoral cell cytoplasm in comparison to the benign epithelial cytoplasm. There was no correlation between the level of IGF-1R expression and tumour stage. However, receptor upregulation was a feature of malignant transformation rather than epithelial cell proliferation where the authors found lower levels of expression in basal proliferative crypts and hyperplastic polyps (5/5). The validity of the result was supported by tissue positive and negative controls, reagent negative controls (where the antibody was peptide-absorbed with a purified receptor protein sequence) and Western blotting where there was complete molecular weight specificity for $\alpha + \beta$ subunits at 220 kDa in tumoral and normal tissue. Northern blotting for IGF-1R mRNA employing specific probes showed a similar difference between colonic cancers and normal epithelium. These results show for the first time that IGF-1R upregulation is an important finding in the colonic polyp-cancer sequence, providing a possible mechanism whereby tumoral cells could escape normal epithelial growth control.

Persistent disease is common after surgical treatment of high-grade anal intraepithelial neoplasia

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Introduction: High-grade anal intraepithelial neoplasia (AINIII) may predispose to anal squamous cell carcinoma. One treatment option is surgical resection but effectiveness remains uncertain. We report results of follow-up of patients with AINIII treated with surgical resection.

Methods: During 1989–1996 43 patients with AINIII have been identified. Thirty-one have undergone local excision with intent to cure and followed-up with regular anoscopy. For each patient all macroscopically abnormal disease was resected and the anal defect left open, closed primarily or grafted. At follow-up anoscopy, biopsy of any clinically suspicious lesions was carried out.

Results: Median follow-up was 36 months (range 14–104 months). 17 patients (55%) had histological evidence of incomplete excision at the time of initial resection (16 lateral, two deep margins). 15/17 (48% of the total) had clinical and histological evidence of AINIII on subsequent anoscopy within 1 year. 2/14 patients with completely excised AINIII have subsequently developed clinical and histological evidence of AINIII at 6 months and 32 months postoperatively respectively. No patients developed squamous cell carcinoma after resection.

Discussion: These disappointing results illustrate the difficulty of surgical resection for AINIII, with a high potential for incomplete excision. Even with complete excision, disease may still recur in a proportion of patients.

Photodynamic therapy-induced apoptosis is dose- and cell-type-dependent

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Photodynamic therapy results in cell death by apoptosis or necrosis. Many tumours have genetic mutations which suppress apoptotic mechanisms, such as P53 mutations and bcl-2 overexpression. It is not known which apoptotic pathway is activated by PDT, but such anomalies may result in altered PDT sensitivity. The cell death response to aminolaevulinic acid (ALA)-induced PDT was studied in four cell lines: HT1197 (human bladder cancer), MCF-7, T47D (both human breast cancer) and human microvascular endothelial cells (MVECs). Exponentially growing monolayers of cells in 96 well plates were exposed to 1 mM ALA for 4 hours and treated with violet light (350–450 nm) at an approximate LD_{50} or LD_{90} dose. After 8 hours, cells were stained with propidium iodide and bisbenzamide, to identify necrotic and apoptotic cells respectively, and examined by fluorescence microscopy. The number of viable, necrotic and apoptotic cells were counted in each high power field. Controls for light alone, ALA alone and neither were also assessed. The presence of apoptosis was confirmed by nick-end labelling (TUNEL).

Results:

Cell type	Control		Post-PDT	
	% Apoptotic	% Necrotic	% Apoptotic	% Necrotic
MCF-7 LD_{50}	0 [0]	2.3 [0.7]	0 [0]	25 [4.4]*
T47D LD_{50}	0.4 [0.4]	1.8 [0.66]	0.1 [0.1]	57.5 [9.4]*
HT1197 LD_{50}	2.3 [1.1]	2 [0.8]	55 [6.6]*	7.5 [2.4]*
HT1197 LD_{90}	2.6 [1.1]	0.4 [0.2]	26 [8.3]*	53 [12]*
MVEC LD_{50}	1.6 [0.8]	2.3 [1.3]	11.1 [1.1]*	5.7 [1.2]

Values represent mean [SEM]. No significant differences between controls for light only, ALA only or neither. * denotes statistical significance compared to control, $P<0.05$, Mann–Whitney test, $n=9$.

The death response to ALA-induced PDT is both cell-type- and dose-dependent. The reason for the differential response between cell lines is not understood but may reflect underlying genetic modifications to apoptotic mechanisms. The predominance of necrosis at higher PDT doses may reflect severe cellular disruption overriding the ordered apoptotic response. Further work is needed to assess the effect of apoptosis gene mutations on PDT response.

Combination cytokine and suicide gene therapy results in enhanced tumour regression and the regression of distant metastases

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Suicide gene therapy results in the regression of localized tumours. *In vivo*, tumour regression is mediated by a localized anti-tumour immune response. The aim of this study was to determine if tumour regression could be enhanced by strategies designed to upregulate the immune response. Such

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In addition, the relative importance of the parameters changed for each time interval predicted.

Neural networks provide a more powerful, robust and flexible tool for the prediction of outcome in breast cancer. The greater accuracy provided by neural network analysis will facilitate the planning of adjuvant treatment and follow-up for patients with breast cancer.

P53 and p16 transfer in pancreatic cancer cells results in decreased proliferation and increased apoptosis

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Background: Pancreatic cancer displays high levels of loss of function of tumour suppressor genes p53 (75%) and p16 (80%), which have a major role in cell cycle control. p16 prevents the hyperphosphorylation of retinoblastoma protein (pRb) thereby promoting G1 arrest. p53 also has a major role in p53-dependent apoptosis. The aim of this study was to replace wild-type p53 and p16 into pancreatic cancer cells and assess the effects on cell growth and cell death.

Methods: Human pancreatic cancer cell lines BxPc3, MIAPACA, Panc1 (all homozygously deleted for p16 and LOH (loss of heterozygosity) p53) and CFPAC1 (wild-type p16) were used. Gene transfer was achieved using adenovirus expressing wild-type p53 or p16 and infection was carried out at a multiplicity of infection of 50–100. Control infections were carried out using adenovirus expressing β-galactosidase. Expression of therapeutic genes was confirmed using PCR, rt-PCR, Western blotting and immunofluorescence. Cell growth curves were plotted for 7 days following gene transfer and were performed in triplicate ($n=3+3$). Cell cycle distribution was assessed using flow cytometry. The presence of apoptosis was confirmed using DNA laddering and quantified by TUNEL assay.

Results: The transfer of wild-type p53 inhibited cell proliferation by 78–91% and the transfer of wild-type p16 inhibited cell proliferation by 66–83% with respect to β-galactosidase controls. The transfer of p16 induced G1 arrest in all cell lines. Following transfer of p53 the apoptosis index was significantly increased ($P<0.004$) when compared with control infection. p16 also resulted in increased apoptosis ($P<0.03$). (Statistics: Mann–Whitney U test.)

Conclusion: Adenoviral-mediated transfer of wild-type p53 and p16 resulted in significant growth inhibition and increased rates of apoptosis in human pancreatic cancer cells. These results indicate a new approach to the therapy of pancreatic cancer.

Parallel session I—breast

The clinical and biochemical outcome in patients with advanced breast cancer treated with anastrozole (Arimidex) following loss of response to tamoxifen and megestrol acetate

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Background: A significant number of patients who receive tamoxifen for advanced breast cancer will have disease progression. New therapies that are effective and with minimal side-effects are needed to treat women with advanced breast cancer.

Aim: To study a subgroup of patients with advanced breast cancer who had progressed or lost response to tamoxifen and/or megestrol acetate and who were subsequently treated by anastrozole, a non-steroidal selective aromatase inhibitor.

Patients and methods: Between October 1996 and September 1997, we prospectively studied 20 patients with advanced breast cancer assessed by clinical examination, biochemically by tumour marker CA15-3 and imaging. All these patients had been treated previously with tamoxifen or megestrol acetate. Those who lost response to either or both of the above were given anastrozole 1 mg/day. Follow-up was at 6 weekly intervals and assessment was on clinical examination, CA15-3 and imaging.

Results: The median age of the patients was 69 years (range 35–93). Median follow-up was 6 months. 15 patients initially presented with early breast cancer. Of these, eight had developed recurrence within the first 5 years and seven after 5 years. Five patients presented initially with advanced disease. Sites of recurrence or metastases were lymph nodes (6), surgical scar (4), skin (8), bone (3) and peritoneum (1). Previous treatment comprised segmental or total mastectomy with axillary clearance (10), primary or adjuvant tamoxifen (20), cytotoxic chemotherapy (1), radiotherapy (4), megestrol acetate (4). Clinical response in the form of shrinkage or disappearance of tumour or nodal mass or healing of fungating tumour was seen in 12 patients. CA15-3 decreased in 7, and returned to normal in one. Three patients died during the follow-up period.

Conclusion: In this study anastrozole has been shown to benefit a larger group of patients than expected from the literature, but this may be due to selection of patients who had been previously controlled with endocrine therapy. Clinical examination and, where this is not feasible, CA15-3 tumour marker may be reasonable outcome measurements to identify such a subgroup which is likely to benefit.

Arm morbidity in 131 women with small breast tumours (up to 10 mm in size) who all had level 2 axillary clearance

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Arm morbidity after surgery for very early breast cancer has rarely been documented.

We report a retrospective study of 131 patients who all had an identical axillary operation (level 2 axillary clearance) and who all had small breast cancers of up to 10 mm in size, pathologically. No patients had radiotherapy to the axilla.

Most patients had been operated on between 1992 and 1996. Median time since surgery was 40 months (range 12–132); 71 patients had non-palpable tumours which were localized pre-operatively; 23 patients had mastectomies and 108 had breast-conserving surgery; 83 patients had radiotherapy to the breast.

Arm volumes were measured on the operated side and compared with the normal side. Repeated circumferential measurements were made and arm volumes calculated. Three arm movements were measured: abduction, internal and external rotation. A subjective assessment of swelling, stiffness, discomfort and numbness was made by questionnaire.

The number of women who had objective swelling of the arm was nine (7%). The number with any restricted arm movement was 24 (18%).

Objective morbidity was correlated with possible causative factors such as time since surgery, the operating surgeon, the handedness of the patient, smoking, the number of nodes removed and involved (19 patients (15%) were node-positive), age, body mass index and subjective morbidity. No correlation was found with any factor studied.

Forty-nine women reported subjective swelling, 54 reported subjective stiffness of discomfort, and 94 reported numbness; 30 patients in total said that their symptoms restricted normal activity in some way. Most had minimal symptoms which did not restrict daily activity. Subjective findings did not correlate with objective findings.

As few patients were node-positive the measured morbidity in this study is more likely to be due to surgery itself rather than axillary disease. Objective morbidity is low and subjective symptoms require further study.

An evaluation of the isotope bone scan in the initial staging of patients with primary carcinoma of the breast

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The value of isotope bone scanning at initial staging of breast carcinoma is contentious, particularly when 'adjuvant' systemic therapy is used and when the detection rate may be very low. For the years 1993–1997, this Unit has incorporated dynamic isotope bone scanning into the baseline staging of new patients (<70 years) with an invasive breast carcinoma. Some with pure DCIS have also been scanned. Other initial staging tests in asymptomatic patients included chest X-ray, blood count, CA15-3, liver function (abdominal ultrasound if abnormal) and breast imaging.

The number of new breast carcinomas has increased from approximately 100 to 250 p.a. with the Unit's development. We have reviewed these staging bone scans and those in symptomatic patients. Bone scans were graded into four categories by a consultant in nuclear medicine (MH): B1, normal; B2, degenerative; B3, suspicious of metastases; B4, diagnostic of metastases.

reviewed these cases with the aim of defining a management protocol for these patients.

These 21 phyllodes tumours occurred in 21 women with a median age of 45 years (range 22–84). All patients had palpable breast lumps at presentation although one patient was referred from the Breast Screening Unit. There were nine right- and 12 left-sided lesions. Pre-operative investigations including clinical assessment, fine-needle aspiration cytology and mammography or breast ultrasound did not give a definitive diagnosis in any case. After initial excision, 13 tumours were classified as benign phyllodes tumour, six as borderline malignant phyllodes and two as malignant phyllodes. Median pathological tumour size was 30 mm (range 10–80). Follow-up time ranges from 1 to 96 months (median 13). Seven patients have had recurrent phyllodes tumours after initial excision. The two patients with malignant phyllodes tumours have both had multiple local recurrences. Two of six patients with borderline malignant lesions and three of 13 patients with histologically benign lesions have had recurrent tumours. Age did not appear to correlate with recurrence, but larger tumour size did appear to be associated with a higher risk of recurrence. Six of the 21 patients were discharged from follow-up by junior staff after initial biopsy, and two of these patients represented with recurrences. This retrospective review suggests a need for a clear management protocol for phyllodes tumours, including a policy for excision of clinically and cytologically benign breast lumps, and with a stated follow-up policy for all phyllodes tumours.

The influence of 'cavity shavings' on local recurrence following breast-conserving surgery

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Randomized clinical trials have demonstrated the efficacy of breast-conserving surgery and adjuvant therapy in the treatment of women with primary operable breast cancer. Local recurrence can, however, be a significant problem. Between 1988 and 1992, in an attempt to assess adequate tumour clearance, 239 patients undergoing breast-conserving surgery had their tumour bed analysed by taking a shaving of the residual cavity wall. Based on the presence of disease in the 'cavity shavings', a selective policy of re-excision was instituted.

Aims: The aim of this study was to compare outcome measures in this group of patients with patients treated by breast-conserving surgery prior to 1988 in whom tumour bed analysis was not performed.

Methods: The case records of 125 patients treated between 1982 and 1987 by breast-conserving surgery (Group A) and 239 patients undergoing breast-conserving surgery and 'cavity shavings' between 1988 and 1992 (Group B) were retrospectively reviewed. Axillary clearance to determine nodal staging was performed in 80% vs 85% (Group A vs B). The incidence of lymph node positivity was 40% vs 29% (Group A vs B). Adjuvant radiotherapy to the breast was administered in 82% vs 78%, chemotherapy in 21% vs 6% and tamoxifen in 42% vs 77% (Group A vs B respectively). Follow-up was determined at a *fixed point* 5 years after initial surgery in all patients and outcome measures assessed.

Results: The local recurrence rates were 16% vs 2%, systemic recurrence rates 19% vs 8% and breast cancer-related death rates 12% vs 8% (Group A vs B respectively).

Conclusions: By adopting a meticulous technique of assessment of tumour bed positivity with selective re-excision, a low local recurrence rate can be achieved. This has coincided with a reduction in systemic recurrence and overall survival and may be due to several factors.

Communication of breast cancer prognosis: women wish to know their chance of cure

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Introduction: Communication of diagnosis and prognosis in breast cancer plays an important part in patient management. Fraction of normal remaining life (NRL) is a novel method of expressing survival in terms of 'cure' rates rather than '10 year survival' rates. We investigated how women would like their diagnosis and prognosis to be given.

Methods: A validated structured questionnaire was administered to 77 women (57 well women (ww) and, after ethical approval, to 12 breast cancer patients (cp)) who had completed active treatment. Additional questions were asked to determine what 'cure' meant to these women.

Results: Mean age was 45 years for well women (range 22–73) and 58 (45–82) for cancer patients. Most women (94%) felt that diagnosis should be given in the clinic rather than over the telephone (6%) and most felt that this should be done by the consultant (ww 70%; cp 83%); the registrar (ww 16%, cp 17%), family physician (ww 40%, cp 0%), breast care nurse (ww 44%, cp 0%). At the time of counselling, 26% of well women and 64% of cancer patients would prefer to be alone, 61% of well women and 27% of cancer patients would prefer to be accompanied by their spouse and 47% of well women and 9% of cancer patients preferred a friend or other family member. No prognosis had been given to seven of the 12 cancer patients, three were given their prognosis in terms of very good/good/not so good and two in terms of 10-year survivals. The vast majority of women wished to know their prognosis and preferred it in terms of cure rates (chance of living their full NRL) in addition to a subjective description (see Table).

Preferred manner of communication of prognosis (options not mutually exclusive)	Well women	Breast cancer patients
• No prognosis	2/57 (4%)	1/12 (8%)
• Descriptive (very good, good or not so good)	36/57 (63%)	5/12 (42%)
• 10-year survival	29/57 (29%)	1/12 (8%)
• 'Cure' rates (full NRL survival)	41/57 (72%)	10/12 (83%)

Living full normal life span (full NRL) was interpreted as 'cure' by 85% (46/53) of well women and 100% (12/12) breast cancer patients. Living at least 80% of NRL was acceptable for 'cure' to 68% (36/53) of well women and 67% (8/12) of breast cancer patients while even 50% of NRL was acceptable for 17% (9/53) of well women and 8% (1/12) of cancer patients, as the meaning of 'cure'.

Conclusion: Women prefer their prognosis in definite terms along with a subjective description. Communication of prognosis in terms of NRL is meaningful, and women in this study accepted 'living full NRL' as 'cure'. It is evident from this study that leaving patients in the dark is no longer a humane option.

Hemimastectomy with immediate implant reconstruction: an alternative method for breast conservation

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The randomized studies of breast conservation surgery (BCS) in the 1980s demonstrated that overall survival in women with breast cancer was not reduced after BCS when compared to mastectomy. The main determining factor for survival is the degree of nodal involvement. However, local control remains a problem in women with advanced loco-regional disease. The traditional management for women with large tumours (relative to the size of the breast) would have been mastectomy. However, such mutilating surgery is unlikely to alter survival, particularly in women with advanced disease.

We present a new technique to conserve the breast in such women. The technique involves a subtotal mastectomy with thick skin flaps, leaving a rim of breast tissue in the inframammary fold. After wide clearance of the local tumour in this manner, a Becker implant is inserted subcutaneously. The inframammary fold remnant allows the reconstructed breast to assume a natural ptosis, unlike traditional subcutaneous mastectomy with subpectoral implants. This technique provides an excellent cosmetic result. Subsequently external beam radiotherapy is given as usual after breast conservation.

This study presents the early data from this series of 24 patients (mean age 48 years) treated since 1994; 19 patients had large primary tumours, of whom 14 had pre-operative chemotherapy. Five women had salvage operations following local recurrence and previous breast conservation. There was no excess morbidity associated with this technique in spite of technical considerations such as the subcutaneous implant position. The mean follow-up period is now 22 months. The mean tumour size was 3.3 cm (after chemotherapy, if applicable). Only one implant was lost 4 months after insertion, following a marked radiotherapy skin reaction and subsequent infection. Only one patient developed local recurrence after 25 months, but this was preceded by systemic relapse. Early data on local recurrence suggest that this technique is associated with an acceptable local recurrence rate.

This new technique should be considered as a simple and quick alternative to mastectomy or more complex reconstruction in women with poor prognosis disease but large local tumours.