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ABSTRACTS

British Association of Surgical Oncology Silver Jubilee Scientific Meeting

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Abstracts of members' papers

Plenary Session I

1. Advanced breast biopsy instrumentation—accurate diagnosis of impalpable mammographic abnormalities

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Introduction: Accurate pre-operative diagnosis of mammographic abnormalities is essential through difficult to achieve, necessitating open surgical diagnostic biopsy in 4035 cases in the UK Breast Screening Programme 1997–98. We have prospectively assessed a multidisciplinary minimally invasive approach to diagnosis of 232 such lesions assessed in our unit over the past year.

Methods: Unit policy was that all patients had initial clinical and ultrasonographic assessment. Initial stereotactic or ultrasound (U/S) guided fine needle aspiration cytology (FNA) was performed by a radiologist and stained using H&E or Papanicalou stains. Further investigation, if required, involved prone table core biopsy or advanced breast biopsy instrumentation (ABBI) excision.

Results:

	Biopsy result		Final diagnosis		Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
	Benign	Malig.	Benign	Malig.				
Stereo FNA ($n=155$)	129	26	105	50	48	98	96	80
U/S FNA ($n=34$)	22	12	17	17	70	100	100	79
Core biopsy ($n=85$)	55	30	50	35	86	100	100	91
ABBI excision ($n=39$)	19	20	19	20	100	100	100	100

PPV = positive predictive value; NPV = negative predictive value; Malig. = malignant; Sens. = sensitivity; Spec. = specificity.

Conclusion: This study identifies that a multimodality diagnostic approach improves pre-operative diagnosis and, where appropriate ultrasound guided FNA is more sensitive and specific than stereotactic FNA. Core biopsy was relatively accurate in the diagnosis of malignancy, though it understaged the disease in three cases. ABBI excision is an appropriate minimally invasive accurate diagnostic tool in the diagnosis of radiologically malignant lesion. Experience from our unit suggests that the sensitivity of other diagnostic investigations is sufficiently low to propose ABBI excision as a cost effective primary intervention in patients with small radiologically malignant lesions.

2. Evidence for the Fas "counter attack" by tumour cells in patients with colorectal cancer

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Background: The Fas receptor (CD95) is expressed by lymphocytes and other cells including colorectal cancer cells. It has been shown that a peritumoural infiltrate of lymphocytes is associated with a good prognosis in colorectal carcinoma. One proposed mechanism is that cytotoxic T lymphocytes (CTLs) expressing Fas ligand activate Fas receptors on the tumour cells, which then induces apoptosis. However, *in vitro* studies have suggested that tumours may be able to mount a "counter attack" against CTLs by downregulating the CTL Fas pathway and enhancing their own Fas ligand, thereby inducing apoptosis in the tumour infiltrating lymhocytes (TILs). However, the relevance of this mechanism in human cancers *in vivo* is not known.

Methods: Colorectal cancers from 94 patients treated for colorectal cancer were examined. Immunostaining was performed for CD8+ (CTLs) cells and Fas ligand using a standard technique with appropriate positive and negative controls. Histological sections were scored by two observers using a standard scoring system assessing the degree of expression for each of these (0—absent/very weak, to 3—strong). Possible prognostic factors were examined using univariate analysis.

Results: A peritumoural infiltrate of TILs was associated with an improved survival ($P=0.01$). High scores of Fas ligand in the tumour cells were associated with low scores of CD8+ lymphocytes around the tumour, and vice versa ($P=0.03$). There was a trend for lower numbers of intratumoural TILs in tumours with increased expression of Fas ligand in the cancer cells. Tumours with prominent staining for Fas ligand tended to have a poorer surival ($P=0.08$).

Conclusion: The results from this study provide evidence to support the concept of a "Fas counter attack" *in vivo* in the tumours of patients with colorectal cancer.

3. Characterization of the oestrogen-responsive finger protein in benign and malignant human breast

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Up to 70% of breast cancers respond to anti-oestrogen therapy, but almost all eventually become resistant and progress. A clearer understanding of the involved pathways could suggest new treatment options. The recently-discovered oestrogen-responsive finger protein (Efp) (Inoue S. *et al., Proc Natl Acad Sci USA* 1993; **90**: 11117–21) contains a RING finger domain seen in a number of tumour-associated proteins, and *efp* maps close to important genes such as the breast cancer gene, *BRCA1*. Efp occurs in the human mammary cell line HBL-100 and mouse mammary epithelium, endometrium, ovary and brain (Orimo A. *et al., J Biol Chem* 1995; **270**: 24406–13).

We have used our own polyclonal antibody to Efp to demonstrate specific

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who have multifocal disease not evident on standard triple assessment. MRI of the breast should be used for the pre-operative planning of surgery for primary breast cancer.

14. Sentinel node biopsy and axillary node sampling—how they compare

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Sentinel node biopsy (SNB) is proposed as a minimally invasive method of staging the axilla. Axillary node sampling (ANS) is an established minimally invasive staging procedure of known efficacy. This study was designed to allow a comparison between SNB and ANS.

Sixty-one patients with operable breast cancer were pre-operatively injected with ^{99m}Tc-labelled colloid (Nanocoll, Amersham Healthcare) immediately adjacent to the tumour. Median interval between injection and surgery was 4h (1–18). At operation a standard four-node ANS was performed following either wide local excision or mastectomy. Each node was then counted using a gamma-detecting probe (C-Trak, Autosuture). The axilla was then examined with the probe for areas of residual high radioactive counts. If found this was excised as a fifth node. Each node was submitted separately to pathology and underwent standard histological assessment.

The sentinel node (SN) could not be identified in four cases. In three of these there was a valid reason. (Two were injected the day before surgery and one had received pre-operative radiotherapy.) The SN was excised as part of the ANS in 72% of cases. In all cases where the SN was not part of the ANS the nodes were negative. One SN excised in a patient with a positive ANS was falsely negative.

This study demonstrates that the sentinel node is frequently missed by ANS. However, when compared with SNB, no patient was understaged by ANS while one patient was understaged by SNB.

15. A new method of localizing impalpable breast lesions

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Background: Accurate localization of suspicious non-palpable breast lesions is essential prior to excision biopsy. Several techniques are available for localization, the most commonly used method being guide wire introduction under mammographic or ultrasonic control. Disadvantages of this method include displacement, migration, breakage and difficulty in placing the wire (anatomy). Dissection to follow the wire can sometimes be difficult, especially if the skin entry site is far from the lesion. The aim of this study is to localize and remove suspicious impalpable breast lesions using Tcm99 and a hand-held gamma probe.

Patients and methods: Seventeen patients with screen-detected impalpable lesions were studied. On the morning of the operation 3–6 MBq of Tcm99 labelled on human albumin were injected into the lesion under ultrasonic or mammographic control. At surgery the hand-held gamma probe (EURO PROBE) was used to detect the area of maximum radioactivity, corresponding to the lesion. This permitted placement of the skin incision directly over it. The excised lesion was then rechecked with the probe to confirm its successful removal and the cavity checked for any residual activity to assure completeness of excision. Specimen mammography was performed followed by routine histological examination.

Results: All 17 lesions were successfully localized and removed (100%). Histology: ductal carcinoma *in situ* (5), invasive carcinoma (7) and benign (5).

Conclusions: We found this new method of localization for excision biopsy of non-palpable breast lesions easier, less time consuming and avoiding inherent problems associated with the guide wire method.

16. Use of digital imaging improves upright stereotactic core biopsy of suspicious microcalcifications

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This study assesses whether the addition of digital check images aids the accurate performance of core biopsy of suspicious microcalcifications using upright stereotactic equipment.

We have compared results from a consecutive series of 104 upright stereotactic 14-gauge core biopsies performed prior to the acquisition of a new digital add-on device with a series of 34 biopsies carried out using the digital facility. The biopsies were performed by experienced radiologists working in our unit over a 32-month period from January 1996, with the digitally aided procedures performed from November 1997 onwards. In all cases specimen radiography was performed and analysed for the presence of radiographic calcifications in the core specimens. Pathological correlation was then carried out with needle histology categorized as normal, benign, atypical ductal hyperplasia (ADH), suspicious of ductal carcinoma *in situ* (DCIS), DCIS or invasive carcinoma. Biopsy was repeated if no calcifications were obtained and core histology was not clearly malignant. Definitive surgical histology was also documented for all cases in which a diagnostic or therapeutic surgical excision was performed.

The use of digital add-on equipment increased the radiographic calcification retrieval from 57/104 (55%) to 28/34 (82%), $P<0.005$. The complete sensitivity in DCIS cases rose from 15/29 (52%) to 11/11 (100%), $P<0.005$. The absolute sensitivity in DCIS cases before digital imaging was 10/29 (34%) and 7/11 (64%) using digital check films (not significant).

We have concluded, therefore, that digital equipment greatly facilitates performance of upright stereotactic core biopsy for suspicious microcalcifications, giving a significantly increased success rate in accurately targeting and obtaining calcifications and, more importantly, a marked improvement in the complete sensitivity for DCIS.

17. Breast reconstruction: comparing five different methods of breast volume measurement

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Breast surgery has become more conservative with regard to the extent of excision due to the improvement in adjuvant therapy. There has also been a great improvement in techniques for reconstruction. For a successful procedure in terms of cosmesis an accurate and reliable figure for breast volume is required. This will enable improved planning and choice of procedure leading to better operative result. There have been numerous methods of breast volume measurement none of which have been compared to each other.

We compared five methods of breast volume assessment: (1) mammography, which has previously been compared to mastectomy specimens; (2) thermoplastic moulding; (3) magnetic resonance imaging; (4) Archimedes principle; (5) anatomical measurements. We also assessed the acceptability of each method to both the patient and clinician. Measurements were performed on 10 women, therefore 20 breasts.

We were able to calculate prediction equations between volume measurements obtained from mammography by the other four methods. (1) MRI, 368 + (0.73 MRI) [±696]. (2) Thermoplastic moulding, 132 + (1.46 thermoplastic moulding) [±442]. (3) Anatomical measurements, 168 + (1.55 anatomical measurements) [±437]. (4) Archimedes principle, 359 + (0.6 Archimedes principle) [±615].

If a mammogram has been performed this is the method of choice. If due to age or lack of pathology no mammogram has been performed than thermoplastic moulding and anatomical measurements should be used. MRI is presently too expensive. Water displacement was the least reproducible and therefore we have advised against its use.

18. Interval cancers—are they different from symptomatic breast cancers?

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Introduction: Interval cancers provide cause for concern for the NHS breast screening programme (NHSBSP). Higher than anticipated rates of interval tumours have been reported by the NHSBSP; in addition, there are conflicting views regarding the survival of women with interval tumours. There have been few data to date reporting the survival of these women in the NHSBSP. This study analyses the tumour characteristics and survival of women diagnosed with interval cancer and compares these to a control group of women with symptomatic cancers.

Patients and methods: 107 women aged 50–67 years were diagnosed with an interval cancer between 1991 and 1996. These data were compared to a control group of 337 women of similar age who were treated for a symptomatic cancer in the same centre between 1987 and 1993. Adjuvant treatment was given according to standard local protocols. All data were collected prospectively onto computerized databases. Differences in tumour

characteristics were analysed by Mann Whitney *U* and chi-squared tests and differences in survival by the log-rank test.

Results: Interval cancers were similar to control tumours for tumour size (mean diameter 23.9 vs. 26.7mm; $P=0.10$, Mann Whitney *U*), tumour grade (mean 2.2 vs. 2.3; $P=0.45$) and number of positive nodes (mean 1.86 vs. 1.82; $P=0.54$). ER positivity was similar in both groups (64.4% vs. 53.1%; χ^2 3.27; $df=1$; $P=0.071$). Breast conservation was more commonly performed for interval tumours (84.1% vs. 64.9%; χ^2 test: χ^2 13.69; $df=1$; $P=0.0002$). The overall survival of both groups was similar (log-rank test χ^2 1.91; $df=1$; $P=0.17$).

Conclusions: These data suggest that interval cancers are similar to symptomatic tumours both in terms of their pathological features and outcome. This supports the recent report[1] suggesting that survival is similar between the two groups. Hence, in the UK, there is little evidence to substantiate the concern that interval cancers fare worse than the symptomatic controls.

Reference

1. Collins S, Woodman CBJ, Threlfall A, Prior P. Survival rates from interval cancer in NHS breast screening programme. *Br Med J* 1996; **316**: 832–3.

19. Randomized trial of the effect of hyperbaric oxygen on response to primary chemotherapy for breast cancer

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Introduction: Hyperbaric oxygen (HBO) has been shown to potentiate the effects of chemotherapy in animal tumour models. However, the effects of HBO on human cancers *in vivo* have been poorly investigated and, to date, no randomized trials have been reported. The aim of this study was to investigate the effects of HBO therapy in potentiating the effects of chemotherapy in patients with breast cancer.

Patients and methods: Thirty were randomized to the study group ($n=15$), receiving either 10 treatments of HBO therapy at 2.4 Atmospheres absolute, 100% oxygen, (in an attempt to induce tumour neovasculature) or to the control group ($n=15$) who did not receive HBO. Patients then were treated with a standard anthracycline-based primary chemotherapy regimen given over 18 weeks. Tumour response was assessed by histological examination of the resected breast tissue following completion of primary chemotherapy and graded according to a previously validated scale (1 = no response to 5 = complete response).

Response: The mean age of the patients was 55 years, ranging from 30 to 73 years. All patients successfully completed the study protocol and tolerated the HBO therapy without problems. Pathological responses were graded as follows:

Path. response	HBO	Control
1	2	3
2	8	3
3	1	5
4	4	2
5		2

Conclusions: Hyperbaric oxygen treatment prior to primary chemotherapy was well tolerated by the patients without complications. However, the use of HBO does not result in a significantly increased pathological response to primary chemotherapy.

20. Radiosurgery: an innovative method of treatment for early breast cancer

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The local treatment of breast cancer appears to have dramatically changed in the last 30 years. However, although the outcome is 'conservative' the intention is 'radical' with the radiotherapy fields encompassing virtually all of the tissues previously excised by radical mastectomy. We propose that this approach be changed. In large studies of breast conservative therapy more than 90% of early breast recurrences have been found to occur at the site of the original primary tumour, whether or not radiotherapy is given and whether or not the margins are involved. This is in spite of the fact that, when mastectomy specimens are examined by detailed radiological–histological correlational methods, small additional invasive or *in situ* cancer foci are found in over 60% of patients, with 80% of these situated remote from the index quadrant. Hence it appears that these additional cancer foci do not in general give rise to local recurrence which more probably develops from the cells that surround the primary tumour, which may be genotypically abnormal although morphologically 'clear'.

We describe here a pilot study using a novel method of radiotherapy to deliver therapeutic radiation to the tissues around the primary tumour immediately following excision, with a degree of precision impossible with an external beam. The Photon Radiosurgery System (PRS) is a simple and ingenious device which in essence is a miniature electron-beam driven *x*-ray source which provides a point source of low energy *x*-rays at the tip of a 3.2-mm diameter tube. The radiation source is surrounded by a conical sheath with a sphere at the tip, enabling delivery of a uniform dose of radiation to a prescribed depth. Since the radiation consists of soft *x*-rays, the beam is rapidly attenuated to reduce the dose to more distant tissue. Depending upon the size of the surgical cavity, various sizes of applicator spheres are available and for each size, the radiation received is proportional to the time the machine is switched on and left *in situ*. A dose of about 5Gy can be delivered in about 30 min at 1cm from the margins of the cavity after wide local excision of the tumour. With this elegant approach the pliable breast tissue around the cavity of surgical excision wraps around the radiotherapy source, i.e. the target is 'conformed' to the source, rather than vice versa.

After completion of this pilot, we propose to undertake a phase II randomized trial comparing conventional radiotherapy with PRS alone, with a potential saving of 6 weeks of external beam radiotherapy time for both the patient and the overstretched resources of radiotherapy departments.

21. Screening of family history patients—what constitutes high risk?

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Aims: Women with a family history of breast cancer attend specialist clinics for high-risk screening. There are currently no uniform criteria for what constitutes increased risk, leading to considerable variation in local practice. A limiting factor of previous studies has been the high number of patients who did not develop cancer, affecting the calculation of incidence data.

Methods: This project is a cross-sectional study of breast cancer detected in a high-risk clinic to evaluate the relative risk of cancer from family history. Women were categorized into lifetime risk of between 1:12 and 1:8 (low risk) and greater than 1:8 (high risk), based on Claus predictive tables. 1677 women attenders with a family history of breast cancer between September 1993 and August 1994 with a mean follow-up of 110 (range 12–357) months were reviewed in this retrospective study. Screening consisted of annual review and mammography. Within each group cancer incidence and tumour variables were obtained and compared with data of family history risk.

Results:

	Low risk	High risk	Total
Patients (*n*)	917	760	1677
DCIS (*n*)	0	3	3
Invasive cancers			
T1a and b	2	3	5
T1c	4	5	9
T2 and larger	3	5	8
Invasive DCIS	9	16	25
Median age at diagnosis	48 (38–61)	43 (26–52)	

9.8/1000 of the low-risk patients compared to 21.1/1000 of the high-risk group developed an invasive cancer or ductal carcinoma *in situ* (DCIS), a difference of 11.2/1000 (95% CI 0.8–23.3). The relative risk in the high-risk group compared to that of the low-risk group is 2.15 (95% CI 0.95–4.82), $P=0.0587$.

Conclusions: The incidence of breast cancer in the low-risk group is only slightly higher than that of the general population. Screening patients with a low risk may be of limited value. The median age of diagnosis would justify screening women earlier than in the NHS Breast Screening Programme. The effect of early diagnosis on survival is unknown and will require a large prospective study.