Breast cancer pathology and predictive factors

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UK patients are willing to donate biological material for sub-studies in clinical trials

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With the establishment of a National Translational Cancer Research Network (NTRAC), the UK is now well placed to become an international leader in building a cancer tissue resource to conduct biological research. However, since the Alder Hey scandal in January 2001, there has been much debate about ethical issues and patient consent relating to the collection and use of tissue samples, and a lack of clear guidance on how specific patient consent for future biological research ought to be.

Since 1999, the Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU) has coordinated 2 major national breast cancer clinical trials where biological material was collected. Thirty five UK centres participated in the START (Standardisation of Radiotherapy) Trial, out of which 27 also opted to take part in a sub-study which involved the collection of one blood sample for each patient to be used for DNA testing. 3585 patients from the 27 participating centres agreed to take part in the main START Trial between January 1999 and October 2002, of whom 2849 (79.5%) also donated a blood sample for future research.

Within the TACT (Taxotere as Adjuvant Chemotherapy) Trial, all UK patients were asked to donate breast tumour tissue for future research. Between February 2001 and February 2003, 3507 patients consented to take part in the main TACT Trial, of whom 3445 (98.2%) also agreed to donate tissue.

	No UK centres taking part) (as % of those taking part in main study)	No patients consenting (as % of those from participating centres)
START (blood samples)	27/35 (77%)	2849/3585 (79.5%)
TACT (paraffin blocks)	102/102 (100%)	3445/3507 (98.2%)

Conclusion: Alder Hey has had little impact on the willingness of patients to donate biological material for research purposes, with the overwhelming majority of patients in clinical trials consenting to this type of research. Any impact made by Alder Hey is likely to be due to concerns of pathologists over releasing material, and/or professional anxieties over ethical and legal issues.

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HER2 analysis in breast cancer by two-colour FISH - significance of chromosome 17 polysomy

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Background: Knowledge of HER2 status is a prerequisite when considering patient eligibility for treatment with trastuzumab (Herceptin): accurate assessment is essential to ensure that all patients who may benefit are correctly identified. The most common techniques to assess HER2 status in routine clinical practice are IHC and FISH. Two different FISH methods for HER2 determination are available: 1. Colour detecting only HER2 gene specific signals e.g. the Inform test (Ventana). 2. Colour with additional visualisation of chromosome 17 centromere e.g. the PathVysion test (Abbott). Only the latter can detect polysomy 17 (an increase of average chromosome 17 counts per cell): convention dictates that the sample be classified as negative if the ratio of HER2 to chromosome 17 is <2.0, although such cases will be positive according to the one-colour technique. At present, the significance of polysomy 17 concerning therapeutic response is unknown.

Method: Tumour specimens from 289 patients were tested for HER2 status by IHC (HercepTest) and FISH (PathVysion) as part of a study evaluating the efficacy of 3-weekly Herceptin in MBC (WO16229). The degree of polysomy was calculated by dividing the number of centromeric specific signals by the number of counted cells (n=60). Low-, intermediate- and high-level polysomy were defined as ratios of 3–4, 4–5 and >5, respectively. All patients within the study were followed until disease progression, with those showing partial or complete response regarded as responders.

Results: 100 patients demonstrated IHC 3+ or FISH+ tumours and were eligible for Herceptin; 96 were assessable for response. The ORR was 21% (n=20). Of the 96 assessable patients, 22 (23%) showed polysomic tumours (13 low level, 3 intermediate level, and 6 high level, respectively) of which 6 responded to Herceptin. These were distributed as follows: 1. low-level polysomy (IHC 3+, FISH+); 2. intermediate-level polysomy (both IHC 3+, FISH-); 3. high-level polysomy (1 IHC 3+, FISH +; 2 IHC 3+, FISH-).

Conclusions: 1. All responders to Herceptin were IHC 3+ (100% specificity for IHC). 2. Frequency of polysomy 17 within patients assessable for response in this study was 23%. 3. 4 of 6 polysomic responders to Herceptin had a FISH- (FISH ratio <2.0), IHC 3+ phenotype. Based on these findings we suggest that if 2-colour FISH is used as the first-line HER2 test, all polysomic FISH- patients should be retested by IHC; IHC 3+ cases are then eligible for Herceptin treatment.

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Anti-metastatic efficacy of clodronate is associated with a decrease in bone turnover

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Treatment for 2 years with oral clodronate (Bonefos® 1600mg has been shown to reduce the incidence of skeletal metastases during therapy in a double-blind placebo-controlled study of almost 1100 women with primary operable breast cancer. The mechanisms by which this is mediated are not yet clear and we therefore examined the relationship between clodronate's effects on bone turnover and the incidence of bone metastases in the same study.

BMD and biochemical markers at diagnosis were not predictive for future bone metastatic risk. Furthermore, within the placebo group, changes in BMD or PINP during the first year of treatment were similar in women who subsequently did or did not develop bone metastases (table). On the other hand, women in the clodronate group who remained free of bone metastases had highly significant decreases in bone turnover (PINP) during the first year, whereas women who developed bone metastases during or following clodronate therapy failed to show suppression of bone turnover (table).

	Placebo		Clodronate		P
Incident bone metastases	Yes	No	Yes	No	
Median changes in 1st year in:					
Spine BMD	-1.6%	-1.7%	+0.1%	+0.2%	<0.001
PINP	+13%	+4%	+19%	-29%	<0.001

We conclude that the reduced risk of bone metastases by clodronate therapy is associated with a significant decrease in bone turnover during the first year of therapy. If these biochemical observations are confirmed, it is possible that markers such as PINP will provide useful outcome measures for both clinical trials and routine monitoring of patients.

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Relationship between tumor markers CEA and CA 15-3, TNM staging, estrogen receptor rate and MIB 1 index in patients with pT1-2 breast cancer.

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Background: Several tumor markers have been proposed to indicate presence and future behavior of breast cancer (BC). However, their sensitivity is usually considered low, especially in patients with early-stage tumors. The aim of this study was to analyze whether a correlation exists between preoperative serum tumor markers CEA and CA 15-3, age of the patients, TNM staging, hormone receptor (ER, PgR) status, and MIB1 proliferation index in patients who underwent curative surgery for primary BC.