PERGAMON

European Journal of Cancer 37 (2001) 939–943

European Journal of Cancer

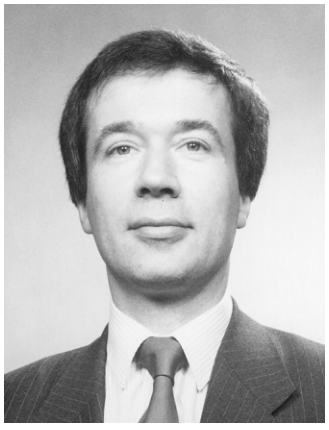
www.ejconline.com

NEWS. . .NEWS. . .NEWS

Barriers to changing clinical practice

Clinical practice is unduly influenced by fashion, culture, personalities and vested interests, delegates heard at the British Oncological Association's recent conference (European Conference on Cancer Strategies and Outcomes (ECSO), 11–14 March 2001, Edinburgh, UK). Speakers called for improved methods of disseminating information from clinical trials.

Dr Fergus Macbeth (Velindre Hospital, Cardiff, UK) said that clinical practice changes "slowly and often idiosyncratically". Some new drugs and procedures are introduced quickly, despite poor supporting evidence, because of intuitive attractiveness, novelty value or strong marketing. Others, though well-proven, may be slow to come into routine practice because the results are not known, not believed, or because of local or national constraints.



Dr Kunkler

Cultural barriers exist between countries. Trials conducted in the States may not to be believed in Europe, and vice versa. Fashion and politics play a part. The fractionated regime for radiotherapy in lung cancer, CHART (Continuous hyperfractionated accelerated radiotherapy), leads to significant improvements in outcome, but has only been implemented in eight UK radiotherapy centres. This is in part due to a shortage of therapy radiographers and in part to weaker support from lobby groups compared to breast cancer. "If the same radiotherapy regime had shown a similar improvement in survival for breast cancer, it would have been more likely to have been implemented," said Dr Macbeth.

Opinion leaders making suggestions at a conference may change delegates' clinical practice in addition to anything in the literature. Further, financial support from pharmaceutical companies may dwarf the amounts available from other sources. Professor Richard Gray (Oxford University, UK) said that meta-analyses could provide definitive answers to clinical questions, but said the answers were not always implemented. Preoperative radiotherapy is regarded as the international standard for rectal cancer, but still only about 80% of patients in the UK receive it.

Dr Macbeth said that the proliferation of journals was making it increasingly difficult for clinicians to keep up with the literature. "We need more effective methods of disseminating important results from clinical trials equivalent to the US National Cancer Institute's 'Clinical Alert'," said Dr Kunkler, president of the British Oncological Association and chairman of ESCO 2001. Further, Dr Jens Overgaard (Aarhus University Hospital, Denmark) suggested that pragmatic trial design could improve trial recruitment and speed up the implementation of results. In the Danish head and neck cancer (DAHANCA) trials, the control arm receives the standard department treatment. This means that if a new treatment shows an improvement, there is no barrier to it becoming the hospital standard.

Professor Michael Baum (University College London, UK) reported on a questionnaire survey of clinical participants in the fastest recruiting breast cancer trial to date (9300 in 3 years in the ATAC) that a simple pragmatic design and good research questions were more factors in securing clinical support than funding.

Professor Mike Richards, the National Cancer Director for England, acknowledged that the poorer cancer outcomes identified in the UK by the EUROCARE group compared to a number of continental European countries has been a major driver to the UK government's investment in cancer services. The high resolution EUROCARE studies in bowel cancer reported by Professor David Forman (Leeds) show that more advanced disease at staging may be a factor in poorer UK outcomes. Similarly there were wide variations in the use of axillary clearance and chemotherapy in young node-positive women.

The American Society for Clinical Oncology (ASCO) and the US NCI have set up initiatives to measure the quality of cancer care delivered to all sections of society, including ethnic minorities. The carefully thought-out methodology includes patients' perspectives and, according to Dr Kunkler, sets a paradigm which others might follow. Also for the future, Professor Karol Sikora (Imperial College London, UK) suggested that increasingly informed and assertive patients will seek out novel therapies and bypass traditional referral patterns, even travelling abroad for treatment.

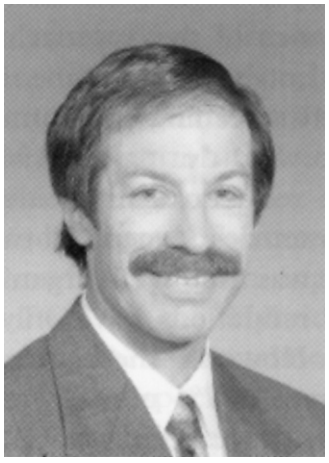
EJC News is compiled by:
Helen Saul
Tel: +44 (0)1865 843340
Fax: +44 (0)1865 843965
E-mail address: h.saul@elsevier.co.uk

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00130-7

IBIS 2 ready to go

The second international breast cancer intervention study (IBIS) could start recruiting later this year (2001) if final ethical and regulatory approval is received. The protocol has received widespread support from throughout the world, said co-chairman Dr Jack Cuzick, head of mathematics, statistics and epidemiology at the Imperial Cancer Research Fund (ICRF), London.

IBIS-2 is to be a 3-arm trial comparing placebo with tamoxifen and with anastrozole. "The new issue is whether anastrozole is better than either tamoxifen or placebo," said Dr Cuzick. The results of IBIS-1, comparing tamoxifen with placebo, have yet to be announced and Dr Cuzick said it is still unclear whether tamoxifen is beneficial in terms of overall risks and benefits.



Dr Cuzick

Countries from all over Europe, Asia, Australasia and South America have expressed an interest in taking part in IBIS-2, which will be led by Dr Cuzick, Dr Tony Howell (Manchester, UK) and Dr John Forbes (Newcastle, Australia). "There is US interest but its not feasible to do the trial when there is an ongoing trial with raloxifene (STAR)," said Dr Cuzick.

American and European trials into chemoprevention of breast cancer have found little common ground so far. The large-scale US trial, the National Surgical Adjuvant Breast Project P1 found that tamoxifen was associated with an almost 50% reduction in new tumours, compared with placebo. The study was halted early and unblinded. Yet preliminary results from studies based at the Royal Marsden Hospital in London, and from an Italian trial, did not indicate that tamoxifen reduced breast cancer incidence and IBIS-1 continued blinded. It closed to recruitment late in 2000, but women are still being followed up.

IBIS-2, which has received approval in principle from ICRF, is to include 10 000 postmenopausal women at high risk of breast cancer. It will include a further 6000 women with DCIS treated either by mastectomy or complete local excision with clear margins. Women will receive 5 years of treatment, either 20 mg tamoxifen, or 1 mg anastrozole or placebo; and the study will have a double-blind, double-dummy design. Recruitment is expected to take 4 years, with a further 5 years of follow-up.

Dr Cuzick said that if IBIS-1 shows definitively that tamoxifen either is or is not an appropriate agent for prevention of breast cancer, women in the 'wrong' arm of IBIS 2 will be re-randomised.

RECIST: Online helpdesk

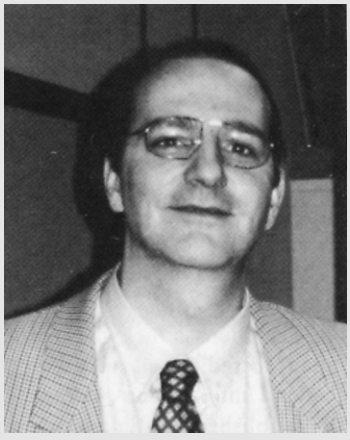
Clinicians measuring solid tumours can now have their queries answered online. A question-and-answer forum has been set up on the EORTC website, and questions are automatically sent to members of the RECIST (Response Evaluation Criteria in Solid Tumours) working party.

The RECIST guidelines (*J Natl Cancer Inst* 2000, **92**, 205–216) were developed by EORTC in collaboration with the National Cancer Institutes of US (NCI) and Canada (NCIC). They have been officially endorsed by the European Medicine Evaluation Agency (EMEA) and widely adopted, including by the US Food and Drug Administration (FDA) and the pharmaceutical industry. They have been translated into French and Japanese and adapted for paediatrics. ''They have been taken up much more widely than we ever anticipated,'' said Dr Patrick Therasse, director of the EORTC Data Center and co-ordinator of the RECIST working party.

RECIST guidelines replaced WHO criteria published in 1979, which had become unworkable and out of date with progress, for example in knowledge of solid tumours and in diagnostics. The RECIST guidelines were always intended to be subjected to continuous assessment, and a revised version will be produced. The question and answer forum is part of the ongoing evaluation process and points raised may be included in the revised version.

The questions addressed to the RECIST working party are discussed by at least 3 members of the working party until a consensus is reached. Professor Verweij, a member of the EORTC working party, said, "Sometimes the responses are quite uniform. Sometimes there are differences of opinions within the same team. It shows that, although the system is workable, it is not completely black and white." Dr Therasse said that further explanation and discussion often helped resolve apparent differences. "We reach consensus for about 90% of questions asked, and the consensus is posted on the website," he said.

Frequently asked questions are already posted on the EORTC website. They range from the straightforward — which axis should be taken into account when measuring the longest diameter? — to the more complex — what happens when target lesions become unmeasurable?



Dr Therasse

Queries should be addressed to *recist@eortc.be* Previous questions may be viewed on the EORTC website: *www.eortc.be/recist* and may also be accessed directly from US NCI and NCIC websites.

Chernobyl linked to UK increase in thyroid cancer

The rise in thyroid cancer among children and young people in the North of England could have been caused by the Chernobyl accident, say researchers in this issue of *EJC* (pp. 1020–1026). They found that in Cumbria, which received the highest doses of radioactive fallout in England, rates of differentiated thyroid cancer were significantly higher after the accident than before.

The researchers studied data from the Northern Region Young Person's Malignant Disease Registry. Rates of thyroid cancer for the region as a whole more than doubled from 1968–1986, before the accident, to the period afterwards, 1987–1997. There were non-significant increases in incidence in Teeside, Northumberland and Tyne and Wear, and no change at all in County Durham. Only Cumbria showed a dramatic 12-fold increase — though the researchers stressed that confidence limits of the study were wide.

Previous studies in areas nearer Chernobyl have shown much greater increases. A 100-fold increase was reported in Belarus, and a 10-fold increase in the Ukraine. However, this is the first study to present data for thyroid cancer among young people outside the Soviet Union for a period ending as recently as 1997.

Concentrations of I-131 in rainwater as high as 784 Bq/l and in goat's milk as high as 1040 Bq/l were recorded in parts of Cumbria, the researchers note, and livestock restrictions enforced in Cumbria immediately after the Chernobyl accident covered 1670 farms in the county. In 1999, a small number of sheep farms were still under restrictions as radiocaesium levels had not fallen consistently below 1000 Bq/kg. However, other parts of Western Europe, notably Scandinavia, received much higher levels of radioactive contamination than Cumbria.

Lead author, Simon Cotterill (Newcastle University, UK) said that other potential explanations for the increase include better detection rates in the later period because of increased awareness and advances in diagnostic technology. The major limitation of the study is the small sample size: just 1 case of thyroid cancer was diagnosed in Cumbria in people under 25 years between 1968 and 1986. There were 6 cases in the subsequent 11 years. Nevertheless, the spatial and temporal changes in incidence were consistent with a causal relationship between exposures to radioisotopes from the Chernobyl fallout. ''Our data is certainly consistent with there being a causal relationship between the Chernobyl accident and the increase in thyroid cancer,'' said Mr Cotterill.

"OUR DATA IS CONSISTENT WITH A CAUSAL RELATIONSHIP BETWEEN CHERNOBYL AND THE INCREASE IN THYROID CANCER."

Dr Cotterill.

Nearly all other post-Chernobyl thyroid cancer studies have focussed on young children because of the acceptance that exposure to radiation mainly causes thyroid cancers in this group, said Mr Cotterill. However, this acceptance is largely based on exposure to external radiation. He said, "We feel that less is known about the radiobiology of chronic exposure to ingested radioiodine, as was seen after the Chernobyl accident. Larger pan-European studies are needed to prove or disprove our findings and investigate any dose-response relationships with changes in incidence of thyroid cancers in young people following Chernobyl," he said.

An accompanying editorial (pp. 945–947) noted that the results of a European study into thyroid cancer are eagerly awaited. It also suggested that the population in Northern England could be followed up for a much longer period. "The risk of radiation-induced thyroid cancer persists for 40 years following exposure, though it does decline after about 30 years," it states.

'No added risk' after benign breast lesion

Women who have a false-positive result from breast screening should be returned to the normal screening programme, say researchers in The Netherlands (*Eur J Surg Oncol* 2001, **27**, 17–20). The risk of developing breast cancer among women with a false-positive result was identical to that of other age-matched controls, they say.

The researchers, based in the Nijmegen region, followed 188 women who had a false-positive screening result between 1985 and 1996, and compared them with age-matched controls from the local cancer registry. After a mean of 7.4 years, there was no significant difference between the groups in occurrence of breast cancer.

It has been suggested that women with excisional biopsies for benign breast lesions should be followed closely because of a higher than average risk of breast cancer. Other researchers have suggested that screening be omitted altogether in this group. The Netherlands group said that omission of screening 'seems hazardous' but that short-interval follow-up mammography is unnecessary after adequate excision biopsy, as confirmed by specimen radiography.

They concluded, "Women who have had excision biopsy for a benign lesion do not have an increased risk of developing breast cancer compared to age-matched controls. Therefore, women who have had a false-positive screening result should be returned to the screening programme as soon as possible."

Chemoprevention in children?

Paediatric oncologists may in future be able to prevent cancers in adults by treating benign precursors in children, a conference heard (3rd London Advanced Paediatric Oncology Course, 12–16 March 2001). Professor Alfred Knudson (Fox Chase Cancer Center, Philadelphia, PA, USA), who first suggested the 'two-hit' model for retinoblastoma, said that another group of hereditary cancers, the phakomatoses, could provide a model for prevention of cancer in future.

In the inherited form of retinoblastoma, one 'hit' is inherited and the other somatic. The two hits together lead to cancer, which develops early: children may be born with retinoblastomas though most cases develop later. In the phakomatoses, one gene is inherited and when the second 'hit' or event occurs, a benign precursor develops, such as polyps of the colon in familial adenomatous polyposis (FAP) or angiomyolipomas of the kidney in tuberous sclerosis. The lesions become malignant only gradually. "Someone with 1000 polyps by the time they are aged 40 might have only 1 to 3 tumours," said Professor Knudson.

There are two opportunities to intervene in this process, he said. Either after the polyps have formed, or before the second event, before the lesions have developed. For example, children with polyposis have few polyps until they reach puberty, after which many develop. "If we have a promising agent, the best time to intervene might be in the first 10 years of life," said Professor Knudson.

"Benign tumours in children with hereditary conditions have never attracted much attention from paediatric oncologists because they are not malignant. My sense is that if we develop agents that can prevent the second event, these diseases should become of interest. Paediatric oncologists may be able to prevent cancer in adults."

Professor Knudson said that adult cancers are often very complicated, which makes them difficult to treat. A pancreatic cancer, for example, might originally have developed from a single clone, but there may be 35 subclones within it. If 30 respond to chemotherapy but 5 do not, the treatment will not be effective. However, in children and young adults, tumours are much more homogenous. There are fewer events and tumours grow so rapidly that it is harder for subclones to flourish.

"It seems to me that therapy is the way to go in children; prevention in adults" said Professor Knudson.

'Re-evaluation of rectal surgery required'

Quality of life issues for patients with rectal cancer need to be reassessed, say German researchers. They found that patients who have a colostomy after rectal surgery have a better quality of life than many of those treated with sphincter-saving techniques (*Ann Surg* 2001, **233**, 149–156).

A vast body of literature suggests the opposite: that patients who have a colostomy have a worse quality of life (QoL). But the German group questioned the validity of this view. Of the 54 papers they identified which were published in English, only 14 were prospective trials, and only 3 used well-established tools for assessing quality of life.

They conducted a prospective trial using the EORTC QLQ C30 questionnaire and the complementary colorectal module CR 38. They included 23 patients undergoing abdominoperineal extirpation (APE) and 50 undergoing anterior resection (AR) for rectal cancer. Patients were assessed before treatment started then 6–9 months and 12–15 months after surgery.

Unexpectedly, APE patients showed a consistent tendency toward a better QoL than the AR patients, especially those undergoing low AR. The differences were mostly nonsignificant, but the researchers said, "APE patients tended to exhibit superior physical, emotional, cognitive, and social function and reported less fatigue, gastrointestinal symptoms, sleeplessness, constipation and diarrhoea. Only for the subscale on body image problems did APE score slightly less favourably." They said, "The consistency in these trends was startling."

One explanation is that, after surgery, many APE patients realise that having a colostomy does not restrict them as much as they had anticipated and their QoL appears better than expected. By contrast, patients who have low AR may feel disillusioned when their continence is compromised.

'Landmark trial' with Herceptin

A study of Herceptin in women with metastatic breast cancer represents "the beginning of an important new era in cancer treatment". Dr Elizabeth Eisenhauer (Queen's University, Kingston, Canada) wrote that the transatlantic work was a 'landmark trial'. (*New Engl J Med* 2001, **344**, 841–842)

The trial (*New Engl J Med* 2001, **344**, 783–792) included 469 women with metastatic breast cancer that overexpressed HER2. They were randomised to receive first line chemotherapy, either alone or combined with weekly intravenous trastuzumab. The combination therapy reduced the relative risk of death by 20% at a median follow up of 30 months. It was also associated with a significantly longer time to disease progression, a higher rate of objective response and longer duration of response.

The researchers, from Germany, Spain, the US and Canada, concluded that the trastuzumab-based combination was effective and said, "If confirmed in additional studies of patients with HER2- positive metastatic breast cancer, our results may affect treatment of this disease."

The most troubling adverse effect of trastuzumab was cardiac dysfunction, which had not been anticipated by preclinical or early clinical trials. It was reported in 27% of the subgroup group receiving an anthracycline, cyclophosphamide and trastuzumab. The researchers said that, given the extremely poor prognosis of patients with HER2-positive metastatic breast cancer, the cardiotoxicity must be weighed against potential clinical benefit. However, it will be a 'critical consideration' in decisions to use trastuzumab postoperatively in patients with early-stage breast cancer.

In the accompanying editorial, Dr Eisenhower said the results of the study are convincing. "They are important because improvements in survival among women with metastatic breast cancer are rare," she wrote. The work has wider implications, she said, since it demonstrates that a targeted molecular therapy can improve outcome. "This trial, which was based on a logical progression of laboratory evidence, will spur investigations of other inhibitors of HER2 and EGFR", she said.

INTERVIEW

ProfessorPat Price is the Ralston Paterson Professor of Radiation Oncology at the Christie Hospital, Manchester, UK, and Director of the Cancer Research Campaign (CRC) PET Oncology Group at the MRC Cyclotron unit, Hammersmith Hospital, London. She is president-elect of the British Oncological Association, Chair of the EORTC Functional Imaging Group and a member of the EORTC Board.

Professor Price

Where did you train?
In medicine, at Cambridge University and King's College Hospital, London. I trained in oncology at the Royal Marsden Hospital, and became a CRC research fellow at the Institute of Cancer Research, Sutton.

Who inspired you?
Professor, now Sir, Mike Peckham was a charismatic figure at the Marsden and was a model for combining clinical and academic work. Tom Connors, always said, 'Be brilliant!' and was one of the driving forces behind the CRC PET oncology unit, he made it happen. Many people at the CRC have been a continuing source of advice and inspiration — Herbie Newell, Trevor Hince and Gordon McVie to name a few. And then, Terry Jones, previous head of PET methodology at the cyclotron unit, who taught me to raise my game in clinical science, and how to put together a big multidisciplinary team. In fact, he inspired me so much I married him!

Why did you choose to work in the field of cancer?
Luck. Soon after qualifying, I reluctantly took a radiotherapy/oncology job as part of my medical rotation. I couldn't believe how interesting it was! It had everything: patient contact, good research interest, lots of variety — I knew this was it.

Did any other branch of medicine appeal?
No.

Might you have done something else altogether?
I wanted to study medicine from being 7 years old, I'm not sure why. At school, for one millisecond I considered studying music — I play the cello — but I'm glad now that I wasn't quite good enough to make it any further than the middle row of an ordinary orchestra. I played in Cambridge University orchestra, and some of the others went on to be professional musicians, but they have such hard lives.

What has been the highlight of your career to date?
In the early 1990s we believed we could use PET to quantify the *in vivo* tumour pharmacodynamics and pharmacokinetics of a drug in a patient — so that we would be able to see where a drug was going to and what it was doing. We were backed by people at the MRC and CRC, and we spent 5 years in the wilderness setting up experiments and collecting data. In 1995 we got to the stage where we knew it would work. It still amazes me: the answer is in the data.

... and your greatest regret?
I have many small regrets — things I could have handled better, time I could have used more wisely — but I am not consumed by them. My brother said that research is all peaks and troughs, I think if you don't get the troughs you are not at the cutting edge, you are not far enough outside of your comfort zone. Doing research has taught me to be philosophical, that every problem is an opportunity — at least on a good day!

If you could complete only one more task before you retire, what would it be?
I would want to see our $20 million Molecular Imaging Centre at the Christie Hospital, Manchester, built and become the best in the world, and to formally establish PET's place in the development of cancer drugs. I've got 22 years before I retire so I hope there's plenty of time!

What is your greatest professional fear?
I fear complacency, mediocrity, conformity, and a lack of risk-taking. I feel that our science is being stifled by managers who don't know the difference between management and leadership, and accountants who don't understand science.

What impact has the Internet had on your working life?
It's great for getting shedloads of information quickly and for fast communication but it's bad for verbal communication. You know something has gone wrong when you are e-mailing the person who sits at the next desk. We should have no-e-mail days!

How do you relax?
I have two young sons who play rugby and on Saturday mornings I stand on the touchline, yelling. Very de-stressing! I also love walking on the Gower Peninsula in South Wales with my husband, who is Welsh. It's really addictive.

Who is your favourite author?
I don't have one. I have lots of books on the go and my favourite depends on my mood.

What do you wish you had known before you embarked on your career?
That to be able to take risks you need to be in control. To do research you have to be a bit of a non-conformist, which can be uncomfortable, particularly within the medical establishment. If I had known this in advance I would have come to terms with it more easily.

What piece of advice would you give someone starting out now?
Go for it! Be true to yourself, don't be in too much of a hurry and enjoy it!

What is your favourite carcinogen?
As a radiation oncologist, I've got to say sunshine! Preferably on a Caribbean island. But this is a complete fantasy — we will probably go to Wales again this year.