PERGAMON

European Journal of Cancer 37 (2001) 817–821

European Journal of Cancer

www.ejconline.com

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Anthracyclines in breast cancer

Data from two French studies suggests upper and lower limits for adjuvant treatment of breast cancer with anthracyclines. One suggests a minimum threshold dose below which treatment outcomes suffer, and the other finds that escalation beyond a critical dose is not beneficial.

The first trial, conducted by the French Adjuvant Study Group (*J Clin Oncol* 2001, **19**, 602–611) included 565 women with operable node-positive breast cancer. After surgery, they all received fluorouracil, epirubicine and cyclophosphamide. Half the group received epirubicin at 50 mg/m^2 (FEC 50); the others received a dose of 100 mg/m^2 (FEC 100).

The overall 5-year survival rate was 65.3% in the group receiving FEC 50 group and 77.4% among those on FEC 100. Disease-free survival was also significantly better and the researchers said their study was "the first to demonstrate a strong benefit" of the increased dose of epirubicin.

The second study (*J Clin Oncol* 2001, **19**, 612–620) compared standard chemotherapy of doxorubicin and cyclophosphamide with an intensified regimen of mitoxantrone and cyclophosphamide with filgrastim. It included 150 women with 10 or more involved axillary nodes. They found no significant difference in either disease-free or overall survival at 5 years. Their work suggested, however, that the subgroup of patients with 15 or more positive nodes may have a decreased risk of relapse.

An accompanying editorial (*J Clin Oncol* 2001, **19**, 599–601) said that invited experts at the US NIH Consensus Development Conference had been asked to define the standard adjuvant therapy regimen for patients with early-stage breast cancer and that these trials contribute to that task. The French Adjuvant Study Group report ''strengthens the case for a minimum threshold dose of anthracycline below which treatment outcomes are inferior.'' The second study ''adds to the growing body of evidence that dose escalation of anthracyclines above a critical dose is not beneficial.''

The meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group in 1995 "confirmed the superiority of anthracyclines in the adjuvant therapy of breast cancer" but, the editorial concluded, "the optimal chemotherapy regimen for women with operable breast cancer has yet to be determined and should continue to be evaluated in clinical trials."

Epidemic ''masked by cervical screening''

A huge increase in risk of cervical cancer has been masked by national screening, says a UK researcher. Consultant cytopathologist, Dr Amanda Herbert (King's College London, UK) found a huge increase in pre-cancer in younger women in the UK (*Cytopathology* 2000, **11**, 471–479). Screening, together with subsequent treatment, has prevented 8 out of 10 cases of cancer.

She analysed national data and found that during a period of time when rates of invasive cancer have halved, they would have more than doubled in the absence of screening. She concludes that the increase may be linked to greater sexual freedom and suggests that the true impact of national screening has not yet been fully recognised in this country. "These findings tell us that just because cervical cancer is now much less common we must not become complacent — the risk is still there — it is crucial that women have regular tests and do not miss the opportunity to reduce that risk."

"WE MUST NOT BECOME COMPLACENT — THE RISK IS STILL THERE."

Dr Anne Szarewski (Imperial Cancer Research Fund Mathematics Statistics and Epidemiology Unit) agreed. Research in her unit has found that the National Health Service cervical screening programme led to 6000 fewer deaths from cervical cancer between 1991 and 1997. "We estimate that by 2025, screening could prevent 5000 cancers a year." she said.

Mike Price: Memorial Service

A memorial service for Professor Mike Price is to be held at 2.30 pm on Friday, 22 June 2001 in the Great Hall, University of Nottingham.

Mike died in November 2000 after a year-long illness with cancer (Obituary, *Eur J Cancer* 2001, **37**, 553–554). Anyone wishing to attend the service will be most welcome.

Please contact Paul.Saunders@nottingham.ac.uk

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

PII: S0959-8049(01)00116-2

MRI could direct treatment of rectal cancer

Modern MRI scans allow surgeons to select patients with rectal cancer who need more radical treatment, say researchers from The Netherlands. They demonstrated that the scans can predict circumferential resection margins accurately and consistently and allow selection of those who would benefit from preoperative radiotherapy, more extensive surgery, or both (*Lancet* 2001, **357**, 497–504).

Incomplete removal of the lateral spread of the tumour is generally accepted as the reason for most local recurrences. Rates decrease greatly when a tumour-free circumferential resection margin of more than 1 mm can be obtained, the researchers say. Surgery alone is often sufficient to achieve local cure and, if a scan could allow reliable selection of patients, preoperative radiotherapy could be limited to those in whom a close resection margin is expected.

The study included 76 patients with primary rectal cancer, assessed preoperatively by MRI scan. Two observers independently measured the distance to the mesorectal fascia. There was high agreement between observers in predicting the distance from the tumour to the mesorectal resection plane. "A tumour-free margin of at least 1.0 mm can be predicted with a high degree of certainty when the measured distance on MRI is at least 5.0 mm," they say.

Most patients with mobile rectal cancers in Europe currently receive a short preoperative course of radiotherapy. "With this approach some patients are undeniably overtreated," the researchers say. "Patients with a very low risk of local recurrence can be operated on without neoadjuvant radiotherapy." In the *Lancet* study, about two-thirds of the patients would not have needed preoperative radiotherapy.

An accompanying editorial (*Lancet* 2001, **357**, 495–496) points out that the finding needs to be confirmed in larger studies. However, it states that if an ongoing Dutch trial of total mesorectal excision (TME) with or without radiotherapy does confirm the role of MRI prediction, ''the need for radiotherapy would be reduced, with reduction in morbidity and cost.''

Electromagnetic fields: still no resolution

Studies in countries other than the UK will be necessary to determine whether exposure to electromagnetic fields (EMFs) can influence the development of cancer. The most detailed study to date found that the question can not at present be completely resolved.

The review was conducted by an independent advisory group to the UK's National Radiological Protection Board (NRPB), chaired by Sir Richard Doll (University of Oxford, UK). It examined work published since its first major review in 1992 and found no good evidence from laboratory experiments that extremely low frequency EMFs are capable of causing cancer. However, there is "some epidemiological evidence" linking magnetic fields with leukaemia in children. "The possiblity remains that intense and prolonged exposures to magnetic fields can increase the risk of leukaemia in children," it concluded.

The report (Doc. NRPB 12 (1) 3-179, 2001. ISBN 0-85951-456-0) concludes that there is no clear evidence of a carcinogenic effect in adults, or of a plausible explanation from experiments on animals or isolated cells. However, some areas of research merit further investigation because of the ubiquitous nature of power frequency electromagnetic field exposure and the concern about possible adverse health effects.

Any cancer risk relates to leukaemia in children and young people and in particular to those with relatively high levels of average domestic exposure to magnetic fields at or above 0.4 microtesla, it stated. This is rare in the UK and relates to about 0.5% of the population.

The advisory group found that nothing would be gained from further residential epidemiology studies in the UK. However, more informative results may come from residential studies in other countries, such as Sweden and Denmark, where exposures may be higher because of differences in the electricity supply and distribution systems. "If parts of the world can be identified where yet greater exposures to children occur frequently and where good quality epidemiological studies are practical, then study of leukaemia risk in relation to electromagnetic field exposures in those places would be valuable."

Further experimental studies were suggested, as were occupational epidemiological studies.

Commenting on the report, Dr John Toy, medical director at Imperial Cancer Research Fund, said that any report that tries to assess the risks is very welcome. "Hopefully public concern will be lessened by the finding that there is no decent evidence to support the theory that domestic electromagnetic fields cause cancer in adults." He said the conclusions support findings from the UK Childhood Cancer Study, which found no conclusive epidemiological evidence of a link between childhood cancer and magnetic fields from power lines. "This news should be a relief for many parents," he said.

''Increasing impact'' of breast screening

Breast screening may soon save more than 1000 lives each year in the UK, researchers say. Their study (*Br J Cancer* 2001, **84**, 423–428) suggests that by 2004 the screening programme will reduce deaths from breast cancer by nearly 20% among women aged between 55 and 64 years.

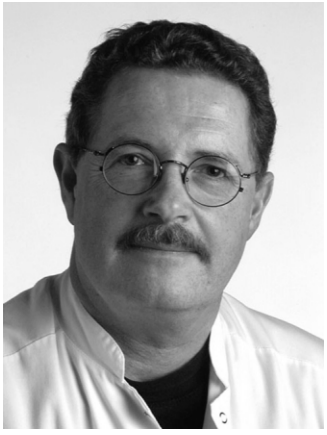
The research was carried out in East Anglia where the introduction of the screening programme in the early 1990s was staggered. This meant that two groups of women could be compared: those diagnosed with cancer before they received an invitation to screening and those diagnosed afterwards, once the screening programme was running. The researchers predicted the outcome for each woman based on the stage of cancer at diagnosis and calculated the expected drop in breast cancer deaths.

The prediction falls short of the 25% target, but, the researchers say, it shows that such a figure is within reach. One of the co-authors, Dr Stephen Duffy (Imperial Cancer Research Fund, London), says the situation may have improved since the study was carried out. "These results do not include screening during the last 5 years, when improvements in screening practice and technology may have saved even more lives."

Danish campaign to boost cancer research

The European Organization for Research and Treatment of Cancer (EORTC) is backing calls by a Danish expert to increase Danish participation in international research. Dr Ole Steen Nielsen, Head of Oncology at Aarhus Kommunehospital, Denmark, chose the international meeting (Aarhus, 5–7 April 2001) held to mark the 25th anniversary of the EORTC's Soft Tissue and Bone Sarcoma Group, to speak out.

Dr Steen Nielsen is chairman of the EORTC's Sarcoma Group and therefore heavily involved with international research cooperation. He said that more Danish participation in international research is vitally important if the 30 000 Danes who are diagnosed with cancer each year, are to have



Dr Ole Steen Nielsen

access to the latest treatments. "This, however, can not happen without further investment from health authorities, as today, many Danish hospitals lack the infrastructure to take part in large-scale international trials," he said.

Sarcomas are rare cancers and affect only 250 Danes per year. The high level of Danish participation in international sarcoma trials means that they have access to the latest treatments and drugs. Not all cancer patients in Denmark have the same opportunity, though, and Dr Steen Nielsen said, "It is important that we are able to offer this to all cancer patients."

Danish hospitals participate in clinical research at the national and the Nordic level, but have been less involved in European research. With a rare group of diseases such as sarcomas, trials need to take in patients from many countries at the same time to be large enough to be relevant. But even for commoner cancers such as of the breast or lung, cross border cooperation is necessary. "Improvements in the treatment of these diseases are often made in very small steps. It is the small discrepancies which are really important and in order to find these we need very large-scale trials," said Dr Steen Nielsen.

An example is the recently-completed EORTC trial of radiotherapy in breast cancer which included 5569 patients. "No single country would have been able to complete a study of that size on their own," he said.

However, international cooperation takes resources and they are not sufficiently available at many Danish hospitals today. Dr Steen Nielsen called for a change. "It is not possible to rely only on the willingness of doctors and other healthcare staff to work for nothing in their spare time. Danish health authorities must make more infrastructure investments in order to make sure that there are sufficient numbers of research nurses, data managers, analysts and paid doctors available," he said.

International cooperation in sarcoma research has led to significant progress. Survival rates for bone cancer have jumped from 15 to 65%. Amputations for soft tissue sarcoma in the limb were once carried out for more than 80% of patients; now it happens for less than 20%. Furthermore, EORTC has been able to attract interest from pharmaceutical companies despite the fact that sarcomas represent such a small part of their potential market. This has allowed EORTC to complete a number of independent treatment trials.

Professor Françoise Meunier, Director General of EORTC, called for increased funds for independent academic research. "This is a tremendously exciting time with a number of promising new compounds and treatments coming through basic research. Yet a lack of collaboration and harmonisation in European clinical research hampers progress in curing patients with cancer."

The EC has issued a set of guidelines, but these are interpreted differently from country to country, which forces the EORTC and any other academic research organisation to spend valuable hours and funds on paperwork. All 15 EU member states have different health insurance systems relating to clinical trials, for instance. "It makes cross-border research complex, expensive and time consuming," said Professor Meunier.

A further problem is the serious lack of funding for independent clinical research. The pharmaceutical industry can not be relied on to establish strategies involving radiotherapy and surgery. Professor Meunier said, "Curing cancer is not simply a question of new drugs but also for making existing drugs less toxic and more efficient and of identifying the best combinations of other therapies. These important tasks are entirely left to academic research."

The EORTC receives no core funding from governments or the EC. It is financed by the private EORTC Foundation — through several national cancer leagues in Europe — the Belgian State Lottery, private contributors and corporations and by funding from the US National Cancer Institute. The total annual budget comes to only €10 million in total.

EORTC trials cover most types of cancer. They are conducted in 31 countries and involve 7000 new patients per year, 2000 medical doctors and 350 university hospitals.

In Europe today, fewer than 10% of medical doctors are familiar with clinical trials and less than 5% of patients take part in clinical trials. Participation in Denmark is among the lowest in Europe: in 2000, only 38 Danish patients took part in trials, compared with 1484 from Holland and 760 from Belgium.

Heidi Amsinck

AWARDS AND APPOINTMENTS

Regulating Affairs at EORTC

Ms An Johanna Baeyens has been appointed Regulatory Affairs Manager at EORTC. She joins the Regulatory Affairs Unit, which ensures that good clinical practice and regulatory measures are applied optimally in EORTC trials conducted in the European Union and in Eastern Europe. Ms Baeyens will maintain close contact on matters relating to academic clinical research with European Institutions, international organisations such as World Health Organisation, and national authorities. She will also give legal advice when problems arise.

Ms An Johanna Baeyens

Ms Baeyens, who is a lawyer, previously worked in the research and development department, and in the legal assistance and medical liability section, of the "Alliance Nationale des Mutualités Chrétiennes'. She has worked for a law firm at the Brussels bar and as a research assistant on French bio-ethical laws for the Katholieke Universiteit Leuven (KU), in Belgium. She is a Belgian national.

She has given lectures on patients' rights at the law faculty of KU Leuven, and at other conferences, and she has participated actively in several meetings organised by the European Commission.

"I find my work at the EORTC very challenging right now as it becomes increasingly clear that more and more health issues can best be regulated at the European level," she says. "Although the organisation of health care provision and health insurance will remain in the competence of the Member States."

The recent European directive on clinical trials harmonised the legal requirements for the protection of clinical trial subjects. Detailed guidelines will be worked out by the European Commission on such issues as the information given to subjects, appropriate safeguards for the protection of personal data, and the collection, verification and presentation of reports of adverse events and reactions. Ms Baeyens says, "I welcome the introduction of the directive on clinical trials. It is only a pity that it does not sufficiently take into account the specific features of academic clinical research."

Academic clinical research is aimed at finding new indications for drugs and the associated risks are of a different order from those in new drug development. This type of research attracts little or no financial support. "The Directive leaves an opening for Member States to foresee exceptional circumstances whereby the sponsor is not obliged to provide the medicinal investigational product for free," says Ms Baeyens.

However, she says, "Research issues like funding and insurance related to clinical research require a European approach and in order to guarantee the further existance of academic clinical research, there is undoubtedly a need for an adequate European legal framework."

"I believe that the EORTC, an internationally recognised network of excellence for developing state-of-the-art treatments for patients with cancer, is in a good position to advise competent health authorities on which treatments to reimburse for today's patients with cancer," says Ms Baeyens.

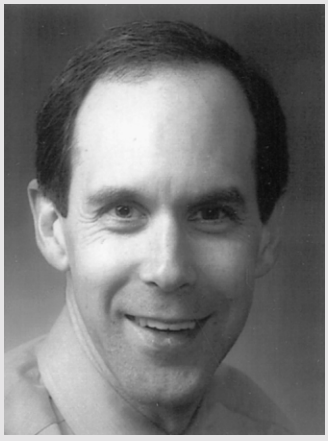
Samantha Christey
EORTC Communications Officer

Development of leukaemia drug rewarded

Dr Brian J Druker (Oregan Health Science University, Portland, OR, USA) has been awarded the Charles Rodolphe Brupbacher Prize for Cancer Research 2001. The award was presented at the Charles Rodolphe Brupbacher Foundation Symposium (14–16 March 2001, Zurich, Switzerland) for ''the preclinical and clinical development of the first ABL-tyrosine kinase inhibitor with proven efficacy in chronic myelogenous leukaemia.''

In recent years, research into signal transduction mechanisms, and how they alter during cells' malignant transformation, has raised hopes that specific inhibitors of these mechanisms would lead to more effective and less toxic cancer treatments. Dr Druker developed the ABL tyrosine kinase inhibitor, STI 571, in collaboration with Novartis Oncology. This compound, now known as Glivec, has been shown to be highly effective in the treatment of chronic myelogenous leukaemia (CML) and acute lymphocytic leukaemia (ALL) carrying a BCR-ABL tyrosine kinase gene rearrangement.

Dr Druker has directed international trials of Glivec involving more than 1000 patients in 30 institutions in six countries. The award, which is worth 150 000 Swiss Francs, is presented biennially. The organisers said, "The potential significance of Dr Druker's work with Glivec now extends beyond leukaemia and represents a strong stimulus for the further development of signal transduction inhibitors with specificity for other malignancies."



Dr Brian Druker

Novartis has submitted applications with the FDA and the European Community. The FDA has given Glivec fast-track status.

INTERVIEW

Dr Alberto Costa is co-founder and Director of the European School of Oncology (ESO), Milan, and a former secretary general of both EORTC and FECS. He is a surgical oncologist, specialising in breast cancer surgery, and is director of the general surgical unit at the Fondazione Salvatore Maugeri, Pavia.

Dr Alberto Costa

Where did you train?
My medical degree and theoretical training is from the University of Milan but I first held a scalpel at a small hospital in Wimbledon, UK, and I remain grateful for the months I spent there. Later, I worked at the Memorial Sloan Kettering Hospital in New York comparing the merits of the Italian quadrantectomy — removing one quarter of the breast — versus the US lumpectomy.

Who inspired you?
Umberto Veronesi, with whom I have worked since 1973. He was attempting to bring Italy back within the realms of science at a time when our laboratories were poor and our best people were going to work in the UK and US. He is now Minister for Health which is the logical evolution of a career dedicated to improving oncology in this country. He has a broad, international outlook, is in touch with the rest of the world; and is also capable of dealing with the minutiae of new research design.

Why did you choose to work in the field of cancer?
I did my degree thesis at the Cancer Centre in Milan and have always been a cancer surgeon. I was initially attracted by the environment, not only as a surgeon but because of my cultural interests. I speak three languages and my first job in 1974 was assisting Umberto Veronesi in the organisation of a UICC congress in Florence.

Did any other branch of medicine appeal?
I started out with romantic ideas about studying tropical medicine and going to work in Africa. I started training in 1968 when we were all under the influence of the move to help the developing world and I thought medicine would be an interesting way of contributing.

Might you have done something else altogether?
I dreamt of a diplomatic career and would have loved to work in international relations. But most of our diplomats belong to the aristocracy, there is tremendous competition and I thought it would be too difficult to find a way in. However, I have to use a lot of diplomacy in my work with European cancer organisations!

What has been the highlight of your career to date?
When we started using plastic surgery techniques to improve the cosmetic results of cancer surgery. First, by reducing the unaffected breast to maintain the body's symmetry, and second, by removing axillary lymph nodes subcutaneously, so as not to leave a scar. It may not sound much, it is not molecular biology, but it is important to many patients and protects their privacy. When they are at the beach or at a ball, nobody need know that they had cancer.

... and your greatest regret?
That I have always been too busy, doing at least two jobs, one as a surgeon, the other running ESO. I would have loved to take a sabbatical and spend a few months working on a thesis.

What is your greatest fear?
Fighting among colleagues. I was lucky to train in a team where for 25 years there was no infighting. It's possibly because Veronesi gave us all so much work to do we had no time to quarrel among ourselves!

What impact has the Internet had on your working life?
It's modest. I use e-mail a lot and my patients often ask questions because of what they've read on the internet. But I still prefer to read journals on paper, as journals, and I prefer physical meetings.

How do you relax?
I really love horseriding, and so does my Irish partner! Listening to classical music, especially Mozart, also helps me relax.

Who is your favourite author?
The Portugese writer Jose Saramago. I discovered him long ago and keep reading his books. He's a great source of inspiration because of his view and experience of life.

What do you wish you had known before you embarked on your career?
How medicine would change. In the early 1970s, medicine resided in the hands of doctors, which had good and bad implications. By the 1980s it had moved into the hands of administrators and insurance companies — the providers — and we are now always looking for guidelines and having to be more and more aware of the costs of treatment. My impression is that none of us has the freedom we expected.

What piece of advice would you give someone starting out now?
Choose a good leader! And if you find yourself in a poisoned environment, have the courage to make a break.

If you could complete only one more task before you retire, what would it be?
To establish a women's hospital in Europe, along the lines of the Brigham and Women's Hospital in Boston, US. It would combine everything: oncology, gynaecology, obstetrics, menopause, depression. It is difficult for a number of boring administrative reasons, but I hope to have the chance to accomplish this.