Pergamon

European Journal of Cancer Vol. 32A, No. 12, pp. 2033–2039, 1996
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Printed in Great Britain.
0959–8049/96 $15.00+0.00

International Cancer News

Compiled by Robert Short, News Editor, London

From The Globe

CALCIUM CHANNEL BLOCKERS ASSOCIATED WITH CANCER

Calcium channel blockers are associated with an increased risk of cancer in people aged 71 years or more, a prospective study of 5052 people living in the U.S.A. shows [1].

The hazard ratio for cancer for patients on calcium channel blockers compared with those not taking them was 1.72 (95% CI 1.27–2.34; P=0.0005). "The association between calcium channel blockers and cancer was found with most of the common cancers," says investigator Dr Marco Pahor, Department of Internal Medicine and Geriatrics, Catholic University, Rome, Italy.

The study population came from Massachusetts, Iowa and Connecticut, and 451 of them were on calcium channel blockers. Demographic variables, disability, cigarette smoking, alcohol consumption, blood pressure, body-mass index, use of other drugs, hospital admissions for other causes, and comorbidity were taken into account.

Death threats

This report adds to the concern about the safety of calcium antagonists which has been angrily debated at cardiology meetings for the last year and a half. Calcium antagonists, some authorities argue, increase the risk of myocardial infarction, gastrointestinal bleeding in hypertensives, and raise mortality in patients with coronary heart disease and hypertension. Some physicians speaking against the class of drugs have received death threats from the public.

Dr Henry J. Dargie of the Clinical Research Initiative in Heart Failure, University of Glasgow, U.K., comments [2], "It is important to keep in perspective the current controversy, which is in danger of developing into a witchhunt. Most doctors who use calcium channel blockers still believe that many patients do benefit from their judicious use. In addition, a recent observational study of 11 575 patients did not support an association between the use of calcium channel blockers and increased mortality" [3].

He argues against their suspension on current evidence. "The only evidence on which that action would be justified is the randomised controlled trial."

1. Pahor M, Guralnik JM, Ferrucci L, *et al.* Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996, 348, 493–497.
2. Dargie HJ. Calcium-channel blockers and the clinician. *Lancet* 1996, 348, 488.
3. Braun S, Boyko V, Behar S, *et al.* on behalf of the Bezafibrate Infarction Prevention Study Participants. Calcium antagonists and mortality in patients with coronary artery disease: a cohort study of 11,575 patients. *J Am Coll Cardiol* 1996, 28, 7–11.

First Death Under Voluntary Euthanasia Law in Northern Territory

Mr Bob Dent, a man with terminal prostate cancer, killed himself in September under the world's first law allowing voluntary euthanasia. He used a computer program to give himself a lethal dose of barbiturates at his home in Darwin, Australia. The assisted-suicide legislation has existed in the Northern Territories of Australia since July, despite opposition from Australia's leading medical association.

Dr Philip Nitschke , a supporter of the legislation and who helped develop the computer program, assisted the man who was in his mid-60s. Medical specialists signed the necessary paper work before Mr Dent injected himself. Under the law, a patient must prove to three doctors, one being a psychiatrist, that they are terminally ill and beyond treatment.

The "Deliverance" program involved the man answering a series of questions on the screen confirming that the course he was about to take was what he wanted to do. Then he touched the final button which triggered the injection. At the time of publication at least five more terminally ill patients were waiting to use the new law to end their lives.

Meanwhile, the Australia Federal Government in Canberra explores ways to ban this highly controversial provincial law.

From Europe

EORTC's Drive to Speed Ethical Approval of Trials

The EORTC is campaigning to reduce the time taken for ethical approvals as part of its drive to speed up the set-up time of clinical trials in Europe.

At present, multicentre clinical trials in the U.S.A. can be started at least 6 months earlier than in Europe. "If we want to activate clinical research in, say 34 centres in 14 countries, we have to agree on a protocol, and we face up to 14 different legal regulations and 34 ethical approvals," says Professor Françoise Meunier, Director General of the EORTC.

With respect to ethical approvals, central procedures exist in France, Denmark and Ireland. Approval from local ethical committees is required for all other countries. The resultant lack of co-ordination can result in considerable delays in setting up trials. Such delays could make European research uncompetitive.

One option is for all countries to agree one approval procedure. Another option is to gain their agreement to accept each other's systems. Professor Meunier has been campaigning to increase mutual recognition of ethical approvals. She says: "It is difficult to foresee a single ethical approval for a Pan-European cancer clinical trial, although that would be more effective. What I am trying to achieve is to extend the current French system, which would allow us to activate a trial in each EU country."

The EORTC enrols more than 7000 patients in phase I–III cancer trials each year. The Data Centre in Brussels has a patient database of 88 000 patients.

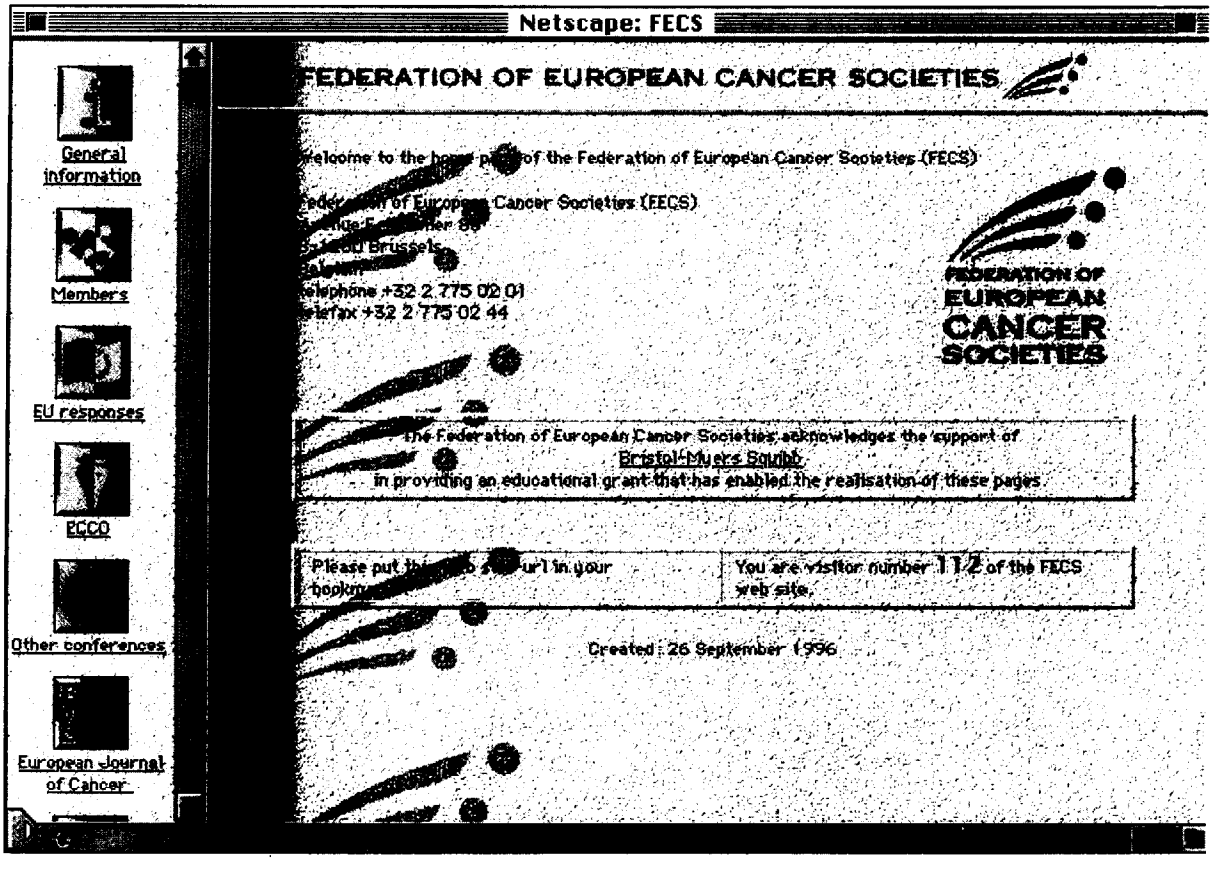
FECS Internet Web Site Now On-line

The Federation of European Cancer Societies (FECS) is pleased to announce that its Internet web site is now "on-line". The URL location is http://www.fecs.be

The web site has been developed by the Federation with the assistance of Hypervision and is supported by an educational grant from Bristol-Myers Squibb. It is best viewed with the web browser Netscape Navigator™ 2.0.2.

The web site contains information on the purpose of FECS, how it is governed, its main activities and the text of the recent responses to European Union consultation documents. A large part of the web site is devoted to ECCO 9 and includes relevant practical and organisational information about conferences including interactive electronic abstract submission and registration forms. There is also a section on other conferences organised by FECS on behalf of its full menbers and these organisations that share its values and beliefs. The web site contains external "hyperlinks" to those full members and related organisations that have their own web site. It also provides facilities to contact FECS by e-mail.

Until it developed its own web site, FECS's presence on the Internet was hosted by the International Union Against Cancer (UICC). Calls to the FECS pages on the UICC server will be rerouted on the FECS web site.



From The Countries

U.K.

Standard Therapy for Epidermoid Anal Cancer Proposed by UKCCCR

Epidermoid anal cancer should be treated with a combination of radiotherapy and 5-fluorouracil (5-FU) and mitomycin, with surgery reserved for those who fail on this regimen.

This regimen should be standard therapy, according to Mr J.M.A. Northover of the ICRF Colorectal Cancer Unit, St Mark's Hospital, Northwick Park, Harrow, U.K., and colleagues in the UKCCCR Anal Cancer Trial Working Party. (UKCCCR stands for the UK Co-ordinating Committee on Cancer Research.)

Before this UKCCCR study, uncontrolled studies had shown that non-surgical management of anal cancer by radiotherapy alone or combined with chemotherapy produced similar local tumour control and survival rates. But the effect on chemotherapy on morbidity was not known.

The investigators write [1]: "This UKCCCR trial demonstrated that the addition of 5-FU and mitomycin to radical radiotherapy substantially improved the chance of avoiding local failure of anal cancer, and hence radical surgery and colostomy. Further, there was a cancer-specific survival advantage. The local failure rate was approximately halved and the proportion of individuals requiring anorectal excision was reduced by a half."

In the study, 585 patients were randomised to receive initially either 45 Gy radiotherapy in 20 or 25 fractions over 4–5 weeks or the same regimen of radiotherapy combined with 5-FU by continuous infusion during the first and the final weeks of radiotherapy and mitomycin on day 1 of the first course.

After a median follow-up of 42 months, 59% of radiotherapy patients had a local failure compared with 36% of chemotherapy patients. This was a 46% reduction in the risk of local failure in the patients receiving chemotherapy (RR 0.54; CI 0.42–0.69; $P<0.0001$). The risk of death from anal cancer was also reduced in the chemotherapy arm, although there was no overall survival advantage. Early morbidity was significantly more frequent in the chemotherapy arm, but late morbidity occurred at similar rates.

1. UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. *Lancet* 1996, **348**, 1049–1054.

DENMARK

Nicotine Inhaler Surrogate to Help Smokers Quit

The first nicotine inhaler has been launched to help smokers break their cancer-causing habits.

The Nicorette Inhaler, made by Pharmacia and Upjohn Inc., is being sold in Denmark as an over-the-counter product. The Danish launch is the first of a series of launches planned through Europe and worldwide. The product has also got approvals for marketing in Italy and The Netherlands.

The inhaler addresses both the physical and behavioural aspects of nicotine dependence. The step away from cigarettes is made shorter than with other nicotine replacement therapies for the many smokers who are dependent on the rituals of smoking. At the same time, the Inhaler provides pure nicotine (without carbon monoxide and tar) in amounts lower than smoking but adequate to relieve the physical craving for nicotine.

Nicotine release is controlled by inhaling air through a mouthpiece (either with shallow or deep puffing) which contains a cartridge loaded with a nicotine impregnated plug. The air becomes saturated with vaporised nicotine which is then mainly absorbed through the lining of the mouth. The mouthpiece and cartridges are available with a reclosable plastic container for carrying convenience.

GERMANY

Cancer Risk 27 Times Higher in Heart Transplant Patients

The risk of developing neoplasia is 27-fold higher in heart transplant recipients compared with non-transplanted people after a mean follow-up of 5 years and 9 months, according to German research. However, the risk of dying due to malignant disease is not significantly higher than in non-immunosuppressed cancer patients.

These were the findings of Dr M. Geiger and colleagues of the Department of Thoracic and Cardiovascular Surgery, Hannover Medical School, Germany. The results of their review of 537 heart transplantations performed at their transplantation centre between 1983 and 1995 were presented at a major transplantation conference in Barcelona.

All patients had received a triple immunosuppressive regimen with cyclosporin, methylprednisolone and azathioprine. A total of 458 long-term survivors (i.e. they were alive over 3 months after operation) were investigated with a mean follow-up of 69 months (range 3–131 months). 46 patients were diagnosed with 48 malignant cancers or premalignant cancers (10.5% of all long-term survivors): 4.37% of all heart transplantation patients had cutaneous cancers; 3.1% lymphomas, 1.1% leukaemias; 0.91% lung carcinomas; 0.65% gastrointestinal cancers; and 0.65% other types of tumours.

Time to diagnosis varied from 8–128 months after transplantation (mean 57 months), the maximum incidence was found between 60 and 72 months.

"Of those patients diagnosed with a malignant disease, 20 died (19% of all late deaths, 43% of all tumour patients). No patient died of complications from cutaneous carcinomas, but 8 patients with lymphoma died (57.1% of all lymphoma patients): three with leukaemia (60%), three lung cancer patients (100%), two patients with gastro-intestinal disease (66%) and two patients with other tumours (66%).

U.K.

Key DNA Repair Gene Isolated

The XPF gene that plays a key role in repairing damage to DNA has been isolated by scientists from the Imperial Cancer Research Fund (ICRF).

Dr Tomas Lindahl, the director of laboratory research at the Imperial Cancer Research Fund, said: "Isolating this gene and purifying the protein enzyme it controls is a landmark in DNA repair research. The gene, XPF, has been the missing piece in a jigsaw puzzle of nucleotide excision repair (NER) genes. Identifying it will enable us to define the way the body's repair system works. It may also help in the future to improve those cancer treatments that work by damaging DNA."

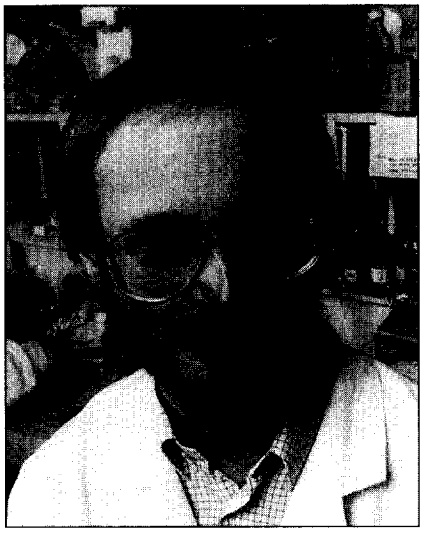
NER genes control production of enzymes that highlight, chop out and repair damage to DNA. Without them cells can mutate as they divide which may lead to uncontrolled cell growth and cancer.

The isolation of XPF was made possible by studying xeroderma pigmentosum, a disease in which people are very sensitive to sunlight and prone to skin cancer. Xeroderma pigmentosum has six forms that involve severe defects in patient's DNA repair systems. The ICRF research team, led by Dr Rick Wood, isolated the gene and enzyme involved in a rare form, XP-F, of which there are only about 12 cases known worldwide.

Said Dr Wood, "Now that we have identified the gene we can make its product in large quantities and work out how it operates. We have started to study the enzymes and we know that it always cuts the DNA in the correct place and at a set point away from the damage. But it is not smart enough to do this without instructions because it is really only a pair of scissors. Somehow, these scissors are guided to the right place by other proteins. Understanding how that works is the next step."

Dr Wood's team worked with teams from Human Genome Sciences Inc. in Maryland and Erasmus University in Rotterdam to search human databases for sequences that might be equivalent to RAD 1, which is a repair gene in yeast. Each organisation found a partial clone and the ICRF team spliced the two together. They then inserted the assembled gene into cells from XP-F patients and found that it corrected the DNA damage in the cells.

Said Dr Wood: "In the future, we may be able to use this information to improve chemotherapy. Some anti-cancer drugs, such as cisplatin, work by damaging DNA. It may be possible to target the XPF gene specifically and turn it off in tumour cells. Then you could make chemotherapy more effective."



Dr Rick Wood

"It may be possible to target the XPF gene specifically and turn it off in tumour cells. Then you could make chemotherapy more effective."

Cancer Research Campaign Inhibitor of Topoisomerase I and II Completes Phase I

Phase I trials for XR5000 have been completed. The phase I clinical trials, undertaken by the Cancer Research Campaign, established the maximum tolerated dose for the drug using a total of 41 patients with advanced stage cancer at centres in the U.K. and 31 patients in New Zealand.

Beating multidrug resistance

XR5000 combines inhibitions of both topoisomerase I and II (which are enzymes involved in cancer cell replication) with the potential to overcome four types of multidrug resistance. The principal clinically measurable side-effect was pain associated with the arm vein infusion of XR5000. The pain was dose-related and ceased shortly after completion of the treatment.

Dr David Secher, Director of Drug Development at the Cancer Research Campaign said, "While remembering that XR5000 is still at a relatively early stage in its development, we are pleased to have successfully completed these phase I trials and to be collaborating with Xenova to progress XR5000 through further clinical development."

The phase II trials, to be sponsored by Xenova (a biopharmaceutical company) at several centres in the U.K. and Europe, are planned for patients with glioblastoma and melanoma, and colorectal, breast and non-small cell lung cancers. Additional phase I studies will also be conducted to explore alternative dosing regimens.

Appointments

New President of Strang Cancer Prevention Center

Dr Michael P. Osborne is the new President of New York's Strang Cancer Prevention Center. He succeeds Dr Daniel G. Miller who became President Emeritus after 26 years in the position.

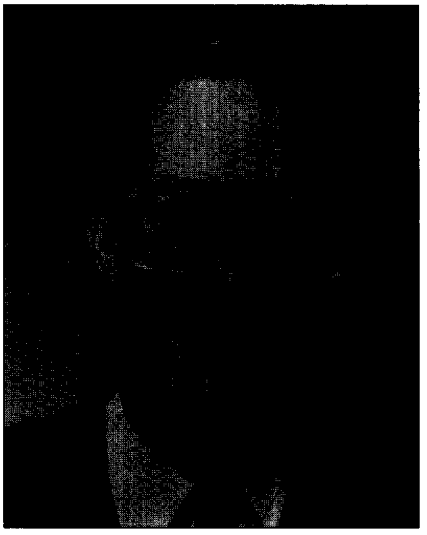
Dr Osborne is originally from the U.K. and previously was Head of the Breast Cancer Research Laboratory and a member of the Breast Service at Memorial Sloan-Kettering Cancer Center, New York. He also is Chief of the Breast Service at the New York Hospital-Cornell Medical Center and Director of the Strang-Cornell Breast Center.

Dr Craig Jordan: Trustee of Worcester Foundation

The Worcester Foundation for Biomedical Research, Shrewsbury, Massachusetts, U.S.A. recently elected Dr V. Craig Jordan to its Board of Trustees.

Dr Jordan is an Editorial Consultant of the *European Journal of Cancer.*

Dr Jordan is based at the Robert H. Lurie Cancer Center at Northwestern University Medical School, Chicago. He conducted the first laboratory studies of tamoxifen at the Worcester Foundation for Biomedical Research from 1972 to 1974.



Dr Craig Jordan

Editorial Consultant of the *European Journal of Cancer* and now Trustee of the Worcester Foundation

•SPECIAL REPORT•

European Society for Therapeutic Radiology and Oncology, Vienna

The European Society for Therapeutic Radiology and Oncology (ESTRO) is the largest society of cancer physicians in Europe, with over 3500 members working in the field of radiotherapy. This report presents highlights of the meeting of ESTRO that took place in Vienna.

EORTC Trial Shows Europe Can "Win Fight Against Breast Cancer"

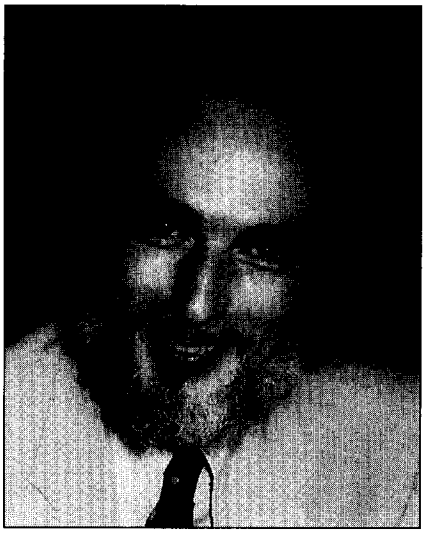
European women getting breast conserving treatment involving radiotherapy and conservative surgery are receiving highly effective therapy, preliminary results of a major EORTC study show.

Over 5500 patients with breast cancer took part in the EORTC study which was designed to establish optimum treatment in breast conserving treatment. In previous trials, breast conserving treatment has been shown to offer similar survival rates to mastectomy in patients with tumours up to 5 cm in diameter. However, variations between study centres on local control rate and cosmetic results were noted. As a result, the EORTC researchers instigated a new quality assurance programme for pathology and radiotherapy to ensure variations between centres were minimised.

The co-ordinators of the study were Professor H. Bartelink (Chairman of the EORTC Radiotherapy Group and Head of the Radiation Oncology Department, The Netherlands Cancer Institute, Amsterdam); Dr J. C. Horiot (Secretary General of the EORTC) and Dr E. van der Schueren (Past President of the EORTC).

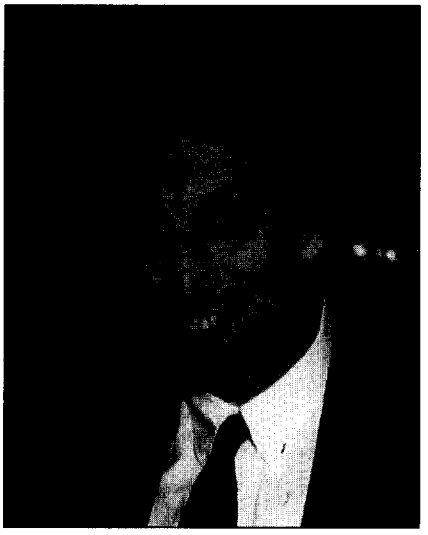
Women in the study all received breast conserving treatment: undergoing tumorectomy, axillary node dissection and radiotherapy (50 Gy) to the whole breast. The patients were then randomised to two groups, one receiving an additional radiotherapy boost dose and the other receiving no additional radiotherapy.

Professor Bartelink said, "The study found that so far there has been very little local recurrence of the



Professor Jean Claude Horiot

President of the International Society of Radiation Oncology and Chairman of the Radiation Oncology Department, Georges François Leclerc, France



Professor Harry Bartelink

Chairman of the EORTC Radiotherapy Group and Head of the Radiation Oncology Department, The Netherlands Cancer Institute, Amsterdam

Professor Jens Overgaard

President of ESTRO and Professor of Clinical Oncology, Denmark

breast cancer. The trial shows that women are receiving excellent treatment which is achieving impressive survival rates. In another 2 years, after long-term patient follow-up, we should be able to say conclusively if the radiotherapy boost dose increases survival even more than the 92% currently achieved at 5-year follow-up. In the meantime, it is clear that the combination of radiotherapy and conservative surgery offers women effective treatment for breast cancer."

Professor Bartelink concluded, "Cosmetically, the most important factor seems to be the size of the biopsy rather than the radiotherapy boost dose. The cosmetic appearance of the breast was determined by a panel of surgeons, radiologists and a lay female representative. The study found that cosmetically, the breast continues to improve during the 3 years following surgery." Professor Jens Overgaard, President of ESTRO and Professor of Oncology, Aarhus University, Denmark, said, "These results give hope to both patients and doctors. Conservative breast cancer treatment, combining radiotherapy and surgery, is saving the lives of many women. With over 90% of patients surviving breast cancer at 5-year follow-up, this trial shows that Europe can win the fight against breast cancer." Implementation of optimal treatment into common clinical practice is now a major challenge.

Terminally Ill Patients are Being Denied Palliative Benefits of Radiotherapy

European terminally ill cancer patients are not being offered radiotherapy as part of their palliative care despite the fact that it is highly effective at relieving pain and other symptoms.

Said Professor Jens Overgaard, President of ESTRO, "Small or single doses of radiotherapy can bring much needed pain and symptom relief to terminal cancer patients, improving their day-to-day living without causing severe adverse effects. Radiotherapy is effective in a range of cancers including bladder, oesophageal and also bone metastases. Despite this, there are still many patients in Europe who are not being offered small doses of radiotherapy as part of their palliative care." He continued, "The exception is the U.K., where there is a tradition of using small dose radiotherapy. This principle is now becoming more widely used across Europe." Professor Overgaard urged oncologists to revise protocols to ensure that all suitable patients are offered such radiotherapy.

Professor Overgaard was speaking at the conference as new studies on this subject were presented.

Metastases

In a European study by Dr Ole Nielsen and colleagues, radiotherapy was given to patients with metastases. The study randomised 241 patients to receive either 8 or 20 Gy. Using pain relief scales, pain relief reduction was 50% and 56% in the 8 Gy and 20 Gy groups, respectively. (There was no significant differences in onset, duration, incidence or degree of pain relief, or quality of life and analgesic consumption between the two groups.)

Oesophagael cancer

Another study, led by Dr Ch. von Briel, Department of Radiation Oncology, University of Berne, Switzerland, investigating the use of high-dose rate brachytherapy (radiotherapy implants) as palliative therapy in oesophageal cancer, found that 91% of the patients had improved swallowing function, with 45% of patients regaining normal swallowing. Forty-eight per cent of patients were able to eat solid food again following treatment. Median survival of patients was 5.3 months. Swallowing difficulties returned in 71% of patients after a median of 4.2 months.

"High-dose rate brachytherapy is an effective, well tolerated palliative procedure for patients with oesophageal cancer and associated swallowing difficulties, relieving discomfort and giving patients back basic abilities, such as eating solid food, which others so often take for granted," said Dr von Briel.

EORTC Trial Review Proves Curative Radiotherapy Benefits Healthy Elderly

Physicians should not refuse to give cancer patients curative radiotherapy based on the patient's age alone, the results of a review of the data from 20 EORTC trials suggest.

The study found that there is no significant difference in toxicity between age groups for each irradiated location, except for grade 2 oesophagitis which is more common in older patients who have undergone thoracic irradiation. Survival was comparable in each age group which allowed late toxicity to be monitored.

The EORTC trials involved 1619 patients with pelvic cancer, 1208 patients with thoracic cancer, and 1589 patients with head and neck cancer. The relationship between age group and the degree of acute toxicity, and whether chronological age had impact on difference, were investigated. Only acute functional mucosal reaction showed a significant trend towards increased toxicity in older head and neck cancer patients. Older patients who received thoracic radiation were found to have limited (< 10%) weight loss, while there were no differences between age-groups for pelvic cancer.

This result provides a lesson for physicians who believe elderly patients are too old to tolerate therapy. Said Professor Pierre Scalliet, Professor of Radiotherapy, Cliniques Universitaires St-Luc, Brussels, Belgium: "Older patients should be evaluated and recommended for radiotherapy on the basis of their general health and not purely on age. Healthy, elderly cancer patients have a right to receive the optimum treatment for their condition and not be denied therapy just because they are older. As the percentage of elderly within European populations rises doctors will be increasingly faced with making treatment decisions for older patients with cancer."

Fractionation Improves Survival in Head and Neck Tumours

Reducing radiotherapy treatment time results in improved survival in lung cancer and improved local tumour control and quality of life in head and neck cancer, recent published trials show. Two of these trials, one a published EORTC study (1), and one a U.K. study known as CHART, have been noted previously in the last two issues of *International Cancer News*. These major studies were discussed considerably at the meeting.

A Danish study, led by Professor Jens Overgaard, Professor of ESTRO, has also found that reducing the time over which radiotherapy was given resulted in a significant benefit in tumour control. There were also survival benefits though these were not statistically significant.

Said Professor Overgaard, "By controlling head and neck tumours, physicians can save patients' organs and make a significant improvement in their quality of life. Both hyperfractionation and accelerated fractionation can be used to improve local tumour control. Hyperfractionation is currently the most reliable regimen for local control though the new trials show that accelerated fractionation is a valid treatment option. More research is now needed to find accelerated fractionation schemes which give the benefits of such treatment without increasing late toxicity," said Professor Overgaard.