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HPV vaccination in Europe

The UK has become the 9th country in Western Europe to recommend routine vaccination against the human papillomavirus (HPV). It follows Austria, Germany, Italy, France, Norway, Luxembourg, Belgium and Switzerland, which have previously recommended vaccination programmes for pre-adolescent girls. Similar recommendations have been made in the US, Canada and Australia, and some countries include catch-up programmes for older girls.

The UK's Department of Health has agreed 'in principle' to accept the advice of its expert panel, the Joint Committee for Vaccination and Immunisation (JCVI), that vaccination should be introduced routinely for girls aged around 12-13 years. Agreement is subject to independent peer review of a cost-benefit analysis.

Public Health Minister Caroline Flint said: 'A significant amount of planning is required before we can introduce the immunisation into our programme. However, we are hoping that girls will start being vaccinated from as early as 2008.'

The JCVI's HPV sub-group concluded that 'the additional benefit from herd immunity from vaccination of boys is unlikely to justify the likely cost.' However: 'this will be dependent on attitudes to vaccination, the likely impact of vaccination on genital warts (if the quadrivalent vaccine is chosen) and potential benefits of vaccination to prevent HPV-related disease amongst men who have sex with men.'

Cost effectiveness analyses will take into account whether booster doses are needed later in life, and whether a catch-up programme for older girls is conducted. The JCVI is expected to make its formal recommendation in October, 2007.

The picture may in future be further complicated by evidence of the role of oral HPV infection in oropharyngeal cancer (N Engl J Med 2007;**357**:1944–56). A US/German epidemiological study found that: 'Oral HPV infection is strongly associated with oropharyngeal cancer among subjects with or without the established risk factors of tobacco and alcohol use.'

An accompanying editorial (N Engl J Med 2007;**357**:1993–5) concluded: 'It is worth considering the possibility that some oral, oropharyngeal, and laryngeal cancers might be prevented by HPV vaccination.'

Pregnancy after cancer

New insights into pregnancy outcomes in survivors of childhood cancer are expected to come from a number of large multi-centre studies currently underway. They are reviewed in a forthcoming Current Perspective in EJC, (doi:10.1016/j.ejca.2007.06.011).

Most survivors have normal reproductive function and would be expected to have a successful pregnancy. However, loss of fertility when it occurs is one of the most devastating consequences of cytotoxic therapy for the survivor in the long-term.

Young women who received 'significant cytotoxic insult' to reproductive organs and yet go on to conceive are at high risk of preterm delivery and of having a low birth weight baby.

The authors, Dr. Angela Edgar and Dr. Hamish Wallace (Royal Hospital for Sick Children, Edinburgh, UK) write that radiotherapy can damage uterus and ovaries, and chemotherapy may deplete the ovarian reserve. The risk of early menopause is 13 times higher for survivors of cancer than for their siblings.

Attempts to preserve fertility are being explored, and strategies to protect the ovaries during cancer treatment have been attempted with limited success. 'For prepubertal girls and the majority of young women options remain experimental,' they conclude: 'At the time of diagnosis of cancer, it is important to counsel the patient and the family about the potential risk to future reproductive function.'

Risks to the offspring may be less than has been feared. Two large international studies found that cancer therapies do not confer a greater risk of genetic abnormalities in children born to survivors. Further, once known cancer predisposition syndromes are excluded, 'there is minimal or no increased risk of cancer development in the offspring.'

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doi:10.1016/j.ejca.2007.07.013

NICE recommends brain tumour drugs

The UK's National Institute for Health and Clinical Excellence (NICE) has announced approval for the use of temozolomide (Temodal) and carmustine implants (Gliadel wafers) for patients with malignant brain tumours. Patient organisations, however, fear that some patients may still be denied the therapies.

Carmustine implants were recommended for people with newly-diagnosed high-grade glioma only if 90% or more of the tumour has been removed. The treatment should be given at specialist centres, NICE said, and should be supervised by specialist neurosurgeons with access to magnetic resonance imaging before the operation and technology that can precisely locate the tumour during surgery.

Temozolomide was recommended as a possible treatment for people with newly-diagnosed glioblastoma multiforme who can either carry out all normal activity or at least, can move around and carry out light work.

The decision brings England and Wales into line with most other developed countries. Andrea Sutcliffe, NICE's deputy chief executive, said the recommendations cover the patient groups who will benefit the most. 'This is a good use of NHS resources and it will ensure that patients who suffer from this rare form of cancer are entitled to the same standard of care, regardless of where they live,' she said.

However, a consortium of brain tumour patient groups pointed out that the appraisal took more than 2 years, which meant that 'many of those suffering with a brain tumour had to go without this groundbreaking therapy.' Ella Pybus from Brain Tumour UK expressed further concern about insufficient funding at the local, primary care trust (PCT) level: 'We need assurances now that NICE's recommendations will be implemented uniformly across all of the PCTs so that people suffering from this devastating disease will not be further disadvantaged.'

Medical radiation 'does not cause brain tumours'

Exposure to medical ionising radiation did not significantly increase risk of brain tumours in a German study (EJC 2007 doi:10.1016/j.ejca.2007.06.020). Diagnostic procedures did not increase risk of any tumour type; and although high dose radiation therapy increased risk of meningioma and acoustic neuromas, the increase was non-significant.

The study comprised patients diagnosed with glioma, meningioma or acoustic neuroma and referred to neurosurgical centres in Bielefeld, Mainz, Heidelberg and Mannheim. Controls were randomly selected for population registries in the study area; overall, there were 2532 participants.

Trained interviewers asked participants about their use of mobile phones, transmitters and ham radios; smoking habits; medical histories including diagnostic x-rays and radiotherapy treatment; and occupation, especially where it related to electromagnetic fields or ionising radiation.

Occupational exposure, mostly due to employment in the medical field, was linked with an increase in acoustic neuromas; however, the increase was non-significant. No increases in glioma or meningioma were seen.

The researchers, led by Professor Maria Blettner (Johannes Gutenberg-University of Mainz, Germany) noted that the study, like most case control studies, was liable to recall and selection bias. Further, the number of patients with meningioma was small, reducing its statistical power.

However, the German participants are part of a larger, multinational Interphone study which is expected to shed more light on risks associated with exposure to medical and professional ionising radiation. A planned pooled analysis of data collected by all Interphone study partners 'will circumvent the problem of small numbers of participants,' the authors write.

Electrical killing fields for cancer cells

Promising results with alternating electrical fields have been noted in patients with cancer. Ten patients with recurring glioblastoma multiforme received electrical treatment in a pilot trial and survived twice as long as expected (*Proc Natl Acad Sci USA*, published online June 12, 2007; DOI:10.1073/pnas.0702916104). 250 patients with glioblastoma multiforme are now being enrolled across centres in the US and Europe on a phase III trial.

Electrical fields generated by the Novo-TTField device (NovoCure Ltd, Haifa, Israel) were applied externally through electrodes placed on the scalp for 18 h each day for a maximum of 18 months. The median time to disease progression was 26·1 weeks and half the group remained progression-free at 6 months. The median overall survival was 62·2 weeks and two patients were still progression-free when the study closed. 'One patient is tumour free, as verified by MRI scan, 10 months after stopping treatment', says senior author Yoram Palti at Technion-Israel Institute of Technology, Haifa, Israel (who has a minority holding in Novocure).

Disruption of tumour-cell growth and division is thought to occur because the electrical fields interfere with micro-tubules that form the mitotic spindle and that orientate the mitotic axis.

Survival rates compare favourably with historical data on patients with recurrent glioblastoma multiforme, who typically show disease progression within 20 weeks, and have an overall survival of less than 30–40 weeks. However, "It will be necessary to monitor any cognitive alterations and dermatological toxicity, as well as the effect of treatment on neuropsychological disorders and seizure frequency,' cautions Alba Brandes, Bellaria-Maggiore Hospital, Bologna, Italy.

Kathryn Senior

The full version of this story originally appeared in Lancet Oncol 2007;**8**:578.

EUROFILE

EC Directive could halt the use of MRI

The lack of joined-up thinking between Directorates General (DGs), the bodies within the European Commission which have responsibility for policies in different areas, is often cited as a reason why European legislation is either not as effective as it should be, or ends up having a very different outcome to that which was intended. The Directive on Good Clinical Practice, otherwise known as the clinical trials directive, is an example which is well known to the medical and scientific community. This was intended to harmonise regulations on clinical trials between member states, and thus create a level playing field and protect patients. In fact, it has had exactly the opposite effect and the number of academic clinical trials now carried out in Europe has dropped by about 30%.

Just when we thought that lessons had been learned, along comes another piece of legislation that looks set to cause serious damage to medical practice. The Physical Agents (Electromagnetic Fields) Directive 2004/40/EC appears to be an eminently sensible attempt by DG Employment and Social Affairs to protect workers from exposure to radiation. But 3 years down the line, and only just before the April 2008 deadline for Member States to implement the directive into their own legislation, major concerns are being expressed about its impact on MRI scanning.

Implementation of the directive in its current form would effectively ban the use of MRI for diagnosis and treatment,

'ANYONE WITHIN 1 METRE WOULD BREACH THE EXPOSURE LIMITS'

as well as for research, in all Member States, where currently 8 million patient examinations are carried out per year. It sets limits to occupational radiation exposure which will mean that anyone working or moving near MRI equipment will breach them, thus making it possible for them to sue their employers. Even those maintaining or servicing the equipment may be affected.

The impact assessment which was made at the time the legislation was under discussion did not take into account the social and economic consequences of legislating in this area, says the Alliance for MRI*, a coalition of European Parliamentarians, patient groups, scientists and the medical community who are working to try to delay implementation of the legislation. Says British MEP John Bowis: 'I am extremely concerned that an unintended consequence of the directive, as currently written, would be to make it impossible for health workers to operate MRI scanning machines. That is a nonsense, and must be corrected by the Commission.'

A British study into operator exposure to electromagnetic fields from MRI, published by the Heath and Safety Executive in June 2007, and carried out by Professor Stuart Crozier from Brisbane University, Australia, found that anyone standing within about 1 metre of an MRI scanner in use would breach the exposure limits laid down in the directive. The Commission has accepted this, and said that it will consider the HSE report together with the study it has commissioned itself, and which is due for publication in October 2007, when deciding whether and how to propose amendments to the directive or to extend the implementation period.

But they may already be too late. Slovakia has already implemented the directive, on the grounds that it was based on the assumption that the limits which it sets would have no effect. This means that it is now illegal to carry out MRI in the country, say experts. The European Co-ordination Committee of the Radiological, Electromedical and Healthcare IT Industry, says: 'With regard to the Slovakian situation, lawyers of our corporate company members are studying the consequences for their own technicians as well as industry personnel.'

The directive in its present form poses particular problems to those healthcare staff who care for patients such as children, the elderly, or those who have been anaesthetised, who need help and comfort during scans, says the Alliance for MRI. It will also stop the use of MRI for interventional and surgical procedures, and will curtail cutting edge research, they claim.

It may lead to more exposure to radiation rather than less, says Professor Dag Rune Olsen, who works in experimental radiation therapy at the Norwegian Radiation Hospital, Oslo, Norway, and is chairman of the physics committee of the European Society for Therapeutic Radiology and Oncology (ESTRO). In a statement signed by

'IT IS NOW ILLEGAL TO USE MRI IN SLOVAKIA'

himself and ESTRO President, Professor Michael Baumann, he says: 'The added value that MRI represents to medical diagnostics has been tremendous; also MRI has to a certain extent contributed to a limited increase in the use of ionising radiation in medical imaging (e.g. CT). The latter development is important with respect to radiation-related cancer mortality risks and is as such in line with requirements laid down in EURATOM Directive 97/43 regarding optimisation and justification of medical exposure to ionising radiation.'

It is now compulsory for the European Commission to examine the heath impact of all proposed legislation before it is published, and, in principle, this should prevent such problems in future. Legislation should be based on up to date scientific knowledge. But, say Baumann and Olsen: 'To our knowledge there is no scientific evidence of long-term adverse health effects of exposure to static or fluctuating magnetic fields that are commonly found during MR scanning. Hasty decisions without scientific support will in this case have a severe impact on medical diagnostics and must thus be avoided.'

Mary Rice
Brussels

** Further information about the alliance can be obtained at www.allianceformri.org*

New guidelines 'should be revised'

Renal cancer guidelines issued by the European Association of Urology (EAU) in March 2007 'should be revised' following the release of new data three months later at the American Society of Clinical Oncology (ASCO, 1–5 June, 2007, Chicago, Illinois) annual meeting, experts have said. Professor Martin Gore (Royal Marsden Hospital, London, UK) said: 'In view of new data on the treatment of renal cancer presented at ASCO, the EAU guidelines need to be revisited.'

Professor Stéphane Oudard, (Hôpital Européen Georges Pompidou, Paris, France) agreed: 'This new data is important to take into consideration so that clinicians have the most up-to-date information to guide their practice.'

The EAU guidelines stated that tyrosine kinase inhibitors (TKIs) should be considered as first- or second-line treatment for patients with metastatic renal cell carcinoma (mRCC). Sunitinib malate (Sutent) was advised as first-line therapy in good- and intermediate-risk patients; while sorafenib (Nexavar) was advised as a second-line treatment. In addition, temsirolimus (a specific inhibitor of mTOR) was recommended as first-line treatment in poor-risk patients.

Sunitinib was approved for first-line treatment of mRCC in January 2007 following a phase III study (*N Engl J Med* 2007;**356**:115–25). Researchers led by Dr. Robert Motzer (Memorial Sloan-Kettering Cancer Center, New York, USA) found that median progression-free survival was significantly longer in the sunitinib group (11 months) compared to the interferon alfa-group (5.1 months).

An updated analysis of this trial presented by Dr Motzer suggested that sunitinib prolonged progression-free survival (PFS) across all patient risk groups, including those with the poorest prognosis. Progression-free survival in three prognostic groups for sunitinib *versus* placebo, respectively, was: favourable risk (14.5 months *versus* 7.9 months), intermediate risk (10.6 *versus* 3.8 months) and poor risk (3.7 *versus* 1.2 months). Professor Gore said: 'This new data suggests that sunitinib may also be a reasonable treatment for poorer prognosis patients as well as the patients who have a better outlook, although temsirolimus remains the only agent that has demonstrated an overall survival benefit in poor prognosis patients.' (*N Eng J Med* 2007;**356**(22):2271–81).

A multivariate analysis of pre-treatment features of patients receiving sunitinib in the first-line setting, also presented at the meeting by Dr. Motzer, suggested time from diagnosis to treatment (⩾1 yr *versus* <1 yr), corrected calcium levels (⩽10 *versus* >10 mg/dL) and ECOG PS (0 *versus* 1) are significant prognostic factors for progression-free survival. An analysis of overall survival awaits longer follow up and is anticipated within the next 12 months. In the second-line setting, pooled data from two phase II trials, also presented at ASCO, suggested that significant survival prognostic factors were ECOG PS, time from diagnosis to treatment and haemoglobin levels (13 *versus* <13 g/dL for men and 11.5 *versus* < 11.5 g/dL for women). Professor Gore said: 'This new information still needs to be confirmed in further research but it seems we have a new insight to the factors that may be predictive for survival with a targeted therapy that could help to under-pin risk-stratification for treatment in the future.'

'WE HAVE NEW INSIGHT INTO THE FACTORS THAT MAY PREDICT SURVIVAL'

Other key data presented at ASCO included phase III results of bevacizumab (Avastin) in mRCC. The AVOREN trial found that adding bevacizumab to interferon almost doubled progression-free survival from 5.4 months in patients receiving interferon alone to 10.2 months for patients receiving the combination treatment. There was a trend towards improved overall survival; the overall survival data are still pending. However, there was no difference in progression-free survival in the poor risk group (2.1 months *versus* 2.2 months).

Dr. Ronald Bukowski, (Cleveland Clinic Taussig Cancer Center, Ohio, USA), said: 'Improvement in progression-free survival with bevacizumab in favourable risk groups is similar to that seen with sunitinib. But there was no improvement in the poor risk group with bevacizumab and interferon.' He suggested that current data points to sunitinib for the treatment of all risk groups in the treatment-naïve and first-line setting, with temsirolimus recommended only for those with the poorest prognosis and bevacizumab plus interferon as a potential first-line treatment for those with intermediate or good prognosis.

Final results of the phase III trial of second-line sorafenib in mRCC patients were also presented. Sorafenib received its EU licence in July 2006, but trials in the first-line setting proved negative. The pivotal trial for sorafenib was conducted in mRCC patients who had advanced on or after first-line therapy (*N Engl J Med* 2007;**356**:125–34).

Final results from this trial were presented by Dr Bukowski, a co-author. The study showed that though sorafenib demonstrated a significant progression-free survival benefit, the intention-to-treat final overall survival analysis showed a confounding effect of the crossover of patients from placebo to active treatment.

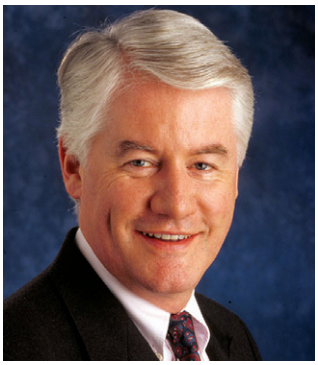
Data from two expanded access programmes for sorafenib and sunitinib presented at the meeting confirmed the safety profiles seen in the phase III clinical trials. Professor Gore, who presented data from the sunitinib expanded access study, said the results suggested that sunitinib showed activity in subgroups of patients not previously studied (non-clear cell carcinoma, patients with brain metastases and elderly patients).

Professor Oudard: 'We are now seeing data that is helping us to understand how we can direct these therapies in terms of which patients are likely to receive the most benefit from which therapies.'

Rhonda Siddall
Freelance medical journalist

PODIUM

The New ECCO



Professor John Smyth (University of Edinburgh, UK) is EJC's editor-in-chief and a former President of ESMO. He serves on the EMEA's Scientific Advisory Committee and chairs the Oncology and Haematology Expert Advisory Group for the UK's Commission on Human Medicine. He has been president of FECS for the past 2 years and is the driving force behind its successor, the European CanCer Organisation (ECCO).

Why replace FECS?

FECS has been an outstanding success. It was formed 25 years ago to bring together all the disciplines involved in research and treatment of cancer. It is best known for organising successful educational and scientific meetings, providing a platform for professionals to learn about each other and encouraging them to interact and work together.

We need to change now because of the growing complexity of cancer in Europe. The success of cancer research means that the range of treatments we can offer would have been unimaginable 25 years ago. Better and more innovative treatments are being given to patients for much longer. This all creates the need for a different forum to integrate and organise cancer treatment and research; we also need to respond to the increasing involvement of patients.

How will ECCO reflect these changes?

ECCO will be larger and more all-embracing than FECS. It will be truly multidisciplinary and will include more organ-based societies; we have invited educational and research organisations ESO and EORTC; along with patient advocacy groups such as Europa Donna and Europa Uomo.

It will have the usual structures of a board and executive committee, but the board will be democratically elected and open to all. ECCO is a non-governmental, not-for profit organisation and its liberal structure reflects its mission.

What are ECCO's aims?

Our mission statement is *Every cancer patient deserves the best*. ECCO exists: to uphold the right of all European cancer patients to the best possible treatment and care; and to promote interaction between all organisations involved in cancer research treatment and care at European level.

This will be achieved by creating awareness of patients' needs and wishes; encouraging progressive thinking in cancer policies, training and education; and promoting European cancer research through the organisation of international multidisciplinary meetings.

The biennial ECCO meetings will continue along with the many other meetings which FECS used to organise or help organise.

How will ECCO address the changing face of cancer?

We can now do more for patients than any civilised society can afford and we need to set priorities. Discussions are taking place within this organisation and without, involving the public and the special section of the public who are patients, along with politicians and professionals.

ECCO is a large organisation and will keep cancer on the political agenda within the European Commission and Parliament. We have a task force which aims to persuade all member states to develop a national cancer plan. These plans are the most appropriate vehicle for addressing priority-setting within individual countries and we have already set up meetings in Romania, Sweden and Spain.

ECCO represents a wide group of interests and is able to help and advise on the development of national cancer strategies. It provides the forum for intelligent, integrated discussion.

What obstacles do you expect?

In setting priorities and devising plans it is clear that one size does not fit all. Slovenia's situation is very different from Sweden's; the German-speaking countries have little in common with southern Italy. There is a huge variation in the available resources and manpower in terms of experience, expertise, and educational levels. Patients in the UK and Scandinavia are likely to be more vocal than many elsewhere. Individual states will develop their own plans and we would expect great variation, but some national strategy is better than none.

How will progress be monitored?

There is a paucity of evidence about the effectiveness of national plans. We have commissioned research on the current state of national cancer plans, where they exist and whether or not they have been effective. It is relatively easy for medics, public health professionals and politicians to talk about national strategies, or for professional societies to roll out guidelines. We need to know whether these strategies and guidelines are gathering dust, or being used effectively.

ECCO will monitor and audit progress at an operational level and answer questions such as whether a waiting list initiative influences the availability of the surgical process, whether the offer of screening programmes are being taken up, etc.

Will ECCO change anything?

ECCO is an exciting development and will provide the platform for debate on all aspects of cancer – whether on the licensing and pricing of new medicines and technologies, a new EC directive affecting cancer research and treatment, or a new set of EMEA policies.

Healthcare in Europe is a complex, changing scene and ECCO will offer the most appropriate resource for influencing the cancer agenda.