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Six-point plan for safer radiotherapy

The American Society for Radiation Oncology (ASTRO) has committed to a six-point patient protection plan intended to improve safety and quality and reduce the chances of medical errors.

The announcement comes in the wake of media reports in the US about serious errors in the delivery of radiation therapy. ASTRO Chair Dr Tim Williams (Boca Raton Community Hospital, Florida, US) said, 'In any area of medicine, and radiation oncology is no exception, even one error is too many. We have been a leader in efforts to improve the culture of radiation safety within our specialty. Any errors, no matter how small, must be reported, understood and used as a tool to further reduce the potential for future errors.'

The ASTRO Board's plan includes:

- Creating a database for reporting linear accelerator- and computed tomography-based medical errors.
- Enhancing the practice accreditation program, and developing modules to address new technologies.
- Expanding educational training programs to include specific courses on quality assurance and safety.
- Developing tools for patients to use in discussions with their radiation oncologist about the safety programs at their centre.
- Further development of ASTRO's connectivity compliance programme to ensure that medical technologies from different manufacturers can safely transfer information.
- Advocating new and expanded federal initiatives.

Split course radiotherapy in NSCLC

A two week break in palliative radiotherapy for patients with advanced non small cell lung cancer significantly reduced patients' symptoms without adversely affecting cancer survival (*Journal of Thoracic Oncology* 2010 *doi:10.1097/JTO.0b013e3181c6eb20*).

In a retrospective analysis, researchers reviewed the medical records of 140 patients. They found that a preplanned two-week break allowed for selection of patients for high-dose palliative radiation, and did not have an adverse effect on survival.

Lead author Dr Su K Metcalfe (University of Rochester, New York, USA) said, 'Balancing symptomatic relief with the side effects of radiotherapy remains a critical element of patient treatment.'

The authors said their finding provides the basis for future large prospective studies evaluating split-course palliative chest radiotherapy against other regimes.

Shorter radiotherapy schedule in breast cancer

A lower overall radiotherapy dose, given in fewer, larger daily doses may be a safe option for women with breast cancer, UK researchers say. They found that hypofractionated regimes did not increase adverse symptoms or result in worse body image compared with the international standard treatment.

They say the results add to the evidence that shorter hypofractionated radiotherapy schedules are equally effective at reducing the risk of further cancer and thus provide better quality for life (*Lancet Oncol 2010 doi:10.1016/S1470-2045(09)-70382-1*).

A total of 2208 women who had received radiotherapy after primary surgery for early-stage breast cancer were recruited from the Standardisation of Breast Radiotherapy Trials (START). They completed quality of life questionnaires and self assessments of body image at intervals for 5 years after treatment.

Adverse change in skin appearance after radiotherapy was the only symptom to differ significantly between the standard and hypofractionated schedules. The researchers said the overall pattern for all adverse effects was similar, with lower or similar rates for the hypofractionated schedules.

An accompanying editorial (*Lancet Oncol 2010 doi:10.1016/S1470-2045(10)-70004-8*) concluded: 'Hopefully the work by this group will inspire both researchers and clinicians to make understanding and assessment of patients' experiences a top priority.'

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Survival benefit after contralateral mastectomy

Contralateral prophylactic mastectomy (CPM) was associated with a small improvement in 5 year survival from breast cancer, US researchers say. The effect was seen mainly in young women with early-stage, oestrogen receptor (ER) negative disease.

Researchers used the Surveillance, Epidemiology, and End Results database to identify 107,106 women with breast cancer who had undergone mastectomy between 1998 and 2003. A subset of 8902 women had also undergone CPM.

CPM was associated with improved disease-specific survival (hazard ratio of death was 0.63). The association was due to a reduction in deaths among women aged 18–49 years with stage I-II ER-negative cancer: 5 year-adjusted breast cancer survival for this group was 88.5% with CPM versus 83.7% without (*J Natl Cancer Inst 2010;* **102***:1–9*).

Lead author Dr Isabelle Bedrosian (University of Texas MD Anderson Cancer Center, USA) said that growing numbers of breast cancer patients are opting for CPM. 'Across the breast cancer community, studies have shown that the utilisation of the procedure is skyrocketing.

'Until now, we've counselled these patients on a very important, personal decision in a vacuum. With our study, our goal was to understand the implications of the surgery and who may benefit.'

Although a causal relationship between survival and CPM was not proven in this study, the researchers said they expect that the survival benefit will increase with longer follow-up.

'Our research found that breast cancer patients over the age of 60 can be reassured that they will not benefit from CPM,' Bedrosian said. Among other populations of women – such as those aged between 50 and 60; or among young women with early stage, ER-positive breast cancer who receive tamoxifen for only 5 years – the findings about CPM are less clear.

'For some additional breast cancer patients, CPM may very well be a medically-appropriate option,' she said.

Pain relief 'is a human rights issue'

Over-zealous regulations are restricting the availability and accessibility of opioid drugs and depriving many cancer patients of adequate pain relief, a pan European study has found.

Researchers say that restricting access to pain relief through formulary deficiencies and regulatory barriers is a breach of patients' human rights and they conclude: 'There is an ethical and public health imperative to address these issues.'

The study, conducted by ESMO and the European Association for Palliative Care, included data from 21 Eastern European and 20 Western European countries.

Access to pain relief was good in some countries, particularly in Western Europe, but in Lithuania, Tajikistan, Belarus, Albania, Georgia and Ukraine, some essential opioid medicines were completely unavailable.

'While most governments allow physicians to prescribe opioids for patients, regulations vary among nations and in many countries, regulations to reduce substance abuse and to restrict the diversion of medicinal opioids into illicit markets unduly interfere with medical availability for the relief of pain. This is the basis for the internationally recognized public health problem of overregulation,' the researchers write (*Annals of Oncology 2010; 21: 615–626*).

Both the World Health Organization (WHO) and the International Narcotics Control Board (INCB) recommend that opioids should be available for cancer patients and that physicians should be able to prescribe opioids according to the individual needs of each patient.

According to the researchers, regulations which contravene WHO and INCB recommendations include: requirements for special patient permits; limiting the authority of some physicians to prescribe; imposing dose limits; limiting the duration of prescriptions to, for example, 7 days' supply; restrictions on opioid dispensing; increasing bureaucratic burdens through the use of complex or poorly accessible prescription forms or complex reporting requirements; and intimidating health care providers and pharmacists by imposing legal sanctions.

One of the authors, Dr Nathan Cherny (Shaare Zedek Medical Center, Jerusalem, Israel) said: 'This is an issue of cancer patients' human rights, and it's not only a legal imperative, but a moral imperative for the WHO and individual European countries to address the findings of our report. At present, cancer patients in a number of countries are suffering unnecessarily as a result of the under-treatment of their pain.'

An editorial in Palliative Medicine was published to coincide with the study (*Palliative Medicine 2010 doi: 10.1177/0269216309360103*). The authors state that a review of the actual laws and regulations needs to precede reform of national policies to identify the excessively restrictive provisions that can be removed: 'In this way, the consensus need to reform national policy will be based on evidence.'

'IT'S A LEGAL AND MORAL IMPERATIVE FOR THE WHO AND EUROPEAN COUNTRIES TO ADDRESS THESE FINDINGS'

Implementation of any reforms – which may be the hardest step – is vital. 'It would be false to state that the inadequate treatment of cancer pain is due entirely to regulatory restrictions,' they write.

'We know from experience that policy change alone does not bring about increased access. We need to address the low priority of pain with health care, inadequate education, exaggerated fear of opioids and addiction, and problems in the supply chain for medications.'

A global pain relief initiative limited to cancer pain risks inadvertently increasing disparities in pain treatment for those suffering from pain related to AIDS and other conditions; broad collaboration will be necessary. The editorial suggests that the International Union Against Cancer (UICC)'s goal of exacting change by 2020 could be achieved 'but it will require appropriate resources, leadership from individuals and their continental and national palliative care associations, and cooperation from government agencies responsible for drug regulation, cancer and HIV/AIDS,' it concludes.

EUROFILE

A snapshot of cancer in Europe

According to the latest estimates *(EJC 2010; 4:765–781)*, in 40 European countries, there were 3.2 million new cases of cancer and 1.7 million cancer deaths in 2008. The estimates are part of a global exercise being conducted by the International Agency for Research on Cancer (IARC) which aims to establish the total cancer burden in 2008. Figures for the rest of the world are expected to become available over the next few months.

Lead author, Mr Jacques Ferlay, said that Europe has a disproportionate share of cancer: 'Europe represents only 7.5% of the world's population, but it carries more than 25% of the total cancer burden. Approximately 22% of cancer deaths occur in Europe. It's partly because the European population is older than the world in general – and cancer kills mainly among older populations. But it's also because people in Europe are at higher risk of cancer because of a lifestyle which has an impact on the common cancers: breast, prostate, colorectal and lung.'

The use of estimates generates up-to-date statistics on incidence and outcome; information for 2008 is not yet generally available. But they are based on the most recent published data and the predictions were therefore short: incidence estimates for 2008, for instance, were based on figures from 2005/6. Mortality changes less rapidly than incidence, so mortality estimates are more robust, Mr Ferlay said.

While the vast majority of countries have national statistics offices which document mortality from cancer, data collection on incidence is patchy across Europe. National cancer registries represent only 30% of the total population. In the *EJC* report, therefore, incidence is estimated either from the most recent available data, or by using models based on incidence as recorded by local registries. The assumption is made that the ratio of incidence to mortality in the local area can be applied nationally, so that the national incidence can be predicted from national mortality figures.

'EUROPE HAS 7.5% OF THE WORLD'S POPULATION, BUT MORE THAN 25% OF THE CANCER BURDEN'

Jacques Ferlay

In Russia, no incidence data at all were available when the research was being carried out, so the researchers had to use this sort of modelling approach to draw up an estimate. 'It was very unsatisfactory. We say in the report that this estimate should be interpreted with caution,' said Mr Ferlay.

Remarkably, since the paper was published, the IARC group has received national incidence data from the Ministry of Health and Social Development of Russia, that back up the researchers' estimation. 'If we compare these new data, the overall reported cancer incidence is quite close to the estimate we made. It's very good news,' said Mr Ferlay.

Even more encouraging than this, is the potential for IARC to work with the Russian government in the future, Mr Ferlay said. 'Russia is a big European country, and it is difficult to estimate the burden across such a large country, particularly without appropriate data from the country itself. We hope to continue our collaboration with the Russian Federation.'

IARC has plans to continue updating these estimates, Mr Ferlay said: 'There's a clear demand for these data. Government and statistical offices always want the most recent data to set priorities in cancer control. Pharmaceutical companies want to know how many cases there will be to treat, and so on. We're intending to publish new data every two years,' he said.

Helen Saul

Key findings: Europe in 2008

- The most common cancers were colorectal (436,000 cases), breast (421,000), lung (391,000) and prostate (382,000).
- The most common causes of death from cancer were lung (342,000 deaths), colorectal (212,000), breast (129,000) and stomach (117,000).
- The incidence and mortality of lung cancer declined almost everywhere in men, although the rates remain high in Central and Eastern Europe. Rates in women are still rising, though, particularly in Northern and Central Europe.
- Decreases in both incidence and mortality from stomach cancer were seen across Europe.
- Breast cancer incidence increased overall, though in UK, Switzerland and Germany, rates in postmenopausal women declined. Mortality rates in many countries have fallen since the mid 1990s.
- The incidence of colorectal cancer had increased modestly in most European countries, although mortality rates in general declined.
- The incidence of prostate cancer almost doubled between 1995 and 2008, especially in countries where PSA testing of older men has become widespread. Mortality decreased over the same period from an estimated ASR (age-standardised rate per 100,000 person-years) of 23.5 to 20.7.
- The burden of gynaecological cancers (uterus and ovary) equalled that of colorectal cancers in women.

Could airport CT scans pose a cancer risk?

Concerns have been raised recently about the safety of the full-body scanners being rushed into service at airports around the world in the wake of the failed Christmas day bomb attack in the USA. Experts maintain that the extremely low levels of radiation used in these scanners are harmless, with more than 200000 scans equating to the level of radiation exposure experienced during a typical CT scan. Perhaps more worthy of attention is whether that one typical CT scan poses a cancer risk.

The US Food and Drug Administration (FDA) certainly think so, and have just proposed a plan to reduce radiation exposure from CT scans based on two main principles—only proceed with a scan if it is necessary, and use the minimum radiation dose required.

Radiation exposure during diagnostic imaging has not previously been a concern because of the low levels used, according to Mahadevappa Mahesh (Johns Hopkins University School of Medicine, Baltimore, MD, USA). However, the doses used in diagnostic imaging are now receiving more attention after a 2009 report by the National Council of Radiation Protection and Measurements (NCRP) on radiation exposure reported that the radiation dose from medical radiography procedures has increased by more than 600% over the past 25 years; an increase that is mainly attributable to an increased number of CT scans (nearly 68.7 million scans in 2007).

'THERE IS A NEED TO STANDARDISE AND CONTROL THE RADIATION DOSES USED IN CT SCANS'

More recent reports in the *Archives of Internal Medicine* indicate that radiation from CT scans needs to be examined more carefully, and repeat CT scans might pose more risk than previously thought. Using risk- projection models that calculated the cancer risk based on the increased number of CT scans done in the US in 2007, investigators estimated that 29000 future cancers could be attributed to CT scans. Of these cancers, 14000 would result from scans to the abdomen and pelvis, 4100 from chest CT scans, 4000 from head scans, and 2700 from chest CT angiography. A second study reported that cancer risk associated with different types of CT scans varied widely, with an estimated one in 270 women (one in 600 men) developing cancer from a CT coronary angiography done at age 40 years, compared with one in 8100 women (one in 11080 men) developing cancer from a routine head CT scan done at the same age. The reports have sparked debate over the need to look more closely at the risks and benefits of CT scans, according to Mahesh, who was a co-author on both studies.

John Boone (University of California Davis Medical Center, Sacramento, CA, USA) agrees. 'Neither of these articles added new knowledge to the field of CT, but they did serve a purpose by alerting both the public and medical community about the potential risk of unchecked CT use.'

'THE REPORTS RAISED THE ALERT ABOUT THE POTENTIAL RISK OF UNCHECKED CT USE'

Determining how many of the CT scans being done at the moment are medically necessary is not easy. 'Most agree there are many studies that probably don't need to be done but it is very difficult to cull these' said Donald Frush (Duke University, Durham, NC, USA).

What everyone agreeson is that it is crucial for patients and their physicians to make informed decisions on when and why to undergo a CT scan. 'Avoid CT scans whenever possible, but when a CT scan is clearly the best diagnostic test for the patient's condition, order it and get it' said Boone.

Along with minimising unnecessary scans, the need to reduce doses when possible is also important, said Frush. Although acknowledging that some variability in radiation dose is expected based on variations in body size, clinical indication, and scanner type, James Brink (Yale University of Medicine, New Haven, CT, USA) agrees that there is now a need to take steps to standardise and control the radiation doses used in CT scans.

One attempt at this has been an accreditation programme for CT scanning established by the American College of Radiology, which requires careful monitoring and control of radiation dose. 'Patients should take care to seek accredited sites for their CT scans' said Brink.

The American Society for Radiation Oncology has also just issued a six-point plan, which includes proposals to establish the first national central database for reporting errors involving CT scanners and other machines that emit radiation. Also among the proposals are plans to significantly improve the practice accreditation programme, and to begin the development of additional accreditation modules specifically addressing new, advanced technologies.

Mary Beth Nierengarten

For more on the **FDA's plans to reduce radiation exposure from CT scans** see http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm200085.htm

For more on the **proposals by ASTRO** see http://www.astro.org

For more on the **NCRP report** see http://www.ncrponline.org/Press_Rel/Rept_160_Press_Release.pdf

For more on the **reports published in the Archives of Internal Medicine** see *Arch Intern Med 2009;* **169:** 2071–77 and *Arch Intern Med* 2009; **169:** 2078–86

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PODIUM

An insight into the changing features of drug approvals

Professor Hubert Leufkens (Utrecht University, the Netherlands) is chairman of the Dutch Medicines Evaluation Board and a co-opted member of the EC's Committee for Medicinal Products for Human Use (CHMP). He is a co-author of a recent EJC paper 'Therapeutic indications in oncology: Emerging features and regulatory dynamics' (EJC 2010 46:471–475)

Does your paper imply a widespread change in the procedure leading to registration?

It is well known that efforts are being made to reduce the time needed for clinical development and for regulatory review. Our findings confirm this trend, which is positive if it implies quicker access to treatment and reduced regulatory delays. A key question for regulators is to assess how mature a clinical package should be at the time of the drug application. Regulatory authorities have to take decisions based on the best available evidence and, when data supporting the approval are not robust, restrictions to the indications are a means of identifying the patient population that may most benefit from the use of the drug, instead of depriving potential patients of an effective treatment. Obviously, when new knowledge becomes available after the approval, regulatory authorities may extend the indications in order to include a larger patient population. What's needed is a sustainable life-cycle approach to the new therapeutic molecule including risk management plans for identifying and minimising possible drug induced harm after marketing approval.

Are you in favour of restricting and later broadening indications?

Restrictions can allow the patient population to be tailored to those who will benefit most from the treatment, strictly based on the evidence provided by registration trials which mostly involve a highly selected population. On the other hand, regulators have to define indications that are applicable to the 'real' patient population. If the population is too selected, it may be difficult to find patients in general practice who can actually benefit from treatment. Paradoxically, we may be faced with a new drug that is an orphan from the patients' perspective.

The more the indication is restricted, the higher the risk of off-label drug use. In this sense, when regulators adopt heavy restrictions on a new drug which represents a unique therapeutic option, the result could be that the regulatory authority itself fuels off--label use. On the other hand, granting an authorisation without sufficient evidence could harm patients.

How can the needs of special populations be safeguarded?

The issue of special populations in clinical trials has been debated at length by the scientific and regulatory community. Actions have already been implemented at the EU level, such as the new paediatric regulation aimed at further stimulating paediatric research during the pre-marketing phase.

In previous work, we suggested that further registration trials could be avoided when consolidated robust evidence is available in a specific population such as children (*Eur J Clin Pharmacol. 2009 Feb;65(2):209–16*).

How does oncology differ from other medical specialties?

There are many advances in oncology – in molecular biology, biomarkers, diagnostics, and so on – and many unmet medical needs. However, the translation of all these scientific developments into clinical practice often lacks the supportive clinical data needed for regulatory approval.

Why do most anticancer drugs have only a single indication?

Our analysis has shown that, contrary to common belief, most anticancer drugs only hold a single indication. This could be because once the drug is on the market, companies may not be interested in extensions if the drug is on standard treatment protocols. Generic competition may make further investments in drug development simply not very attractive from an industry perspective. This tends to lead to widespread off-label prescribing. Another possibility is that, when we compare the wording of indications for new and older oncology drugs, we see a shift towards more detailed and precise patient targeting for the newer products. The indications for the older products were simply phrased more broadly, allowing a wider window for prescribers.

And yet the first-in-class drugs sunitinib, cetuximab and bevacizumab have multiple indications?

Such recently approved drugs may already have multiple indications because of multiple clinical developments, but it also reflects the fact that many modern oncology drugs are mechanism-based. This provides opportunities for more than one clinical application, which means that a compound can be tested in different oncology areas virtually at the same time. This has positive implications in terms of public health, provided that robust evidence is produced.

Were you surprised by any of your findings?

The time needed to add a new indication for a drug has decreased dramatically over the years, down from 81 months in 1996 to 6 months in 2006. This may show how companies have speeded up the clinical development of drugs. Hopefully our findings will provoke useful discussion among the different stakeholders involved in the process, and lead to fruitful alignments between drug developers and the clinic.

Helen Saul