Sunday, 30 October 2005

Opening ceremony

1 FECS Award

Worldwide meta-analyses of breast cancer treatment – EBCTCG 2005 – an update

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Early breast cancer is so common that even moderate differences in long-term survival, if produced by widely practicable treatments, could well prevent many thousands of deaths a year. Reliable detection of moderate survival differences requires both the avoidance of moderate biases and the avoidance of moderate random errors. Large-scale randomised evidence can in principle achieve both these (large numbers ensure small random errors, and randomisation can avoid bias) as long as substantial bias is not introduced into the interpretation of the randomised evidence by unduly data-dependent emphasis on the results from particular trials or particular subgroups. When many different properly conducted trials have addressed much the same therapeutic questions, some are likely, just by chance, to get results more favourable than the truth and some to get results less favourable that the truth. Unduly selective emphasis on just the more promising (or just the less promising) randomised results can then introduce substantial bias. This is best avoided by a collaborative meta-analyses of all the relevant trials in the world, and every 5 years since 1985 the breast cancer trialists of the world have chosen to share their interim results in the hope of limiting such biases and, and equally importantly, limiting the effects of the play of chance. The first two cycles of this EBCTCG collaboration (in 1985 and in 1990) showed that the local and systemic adjuvant treatments of the 1970s and 1980s could produce small but definite effects on 5-year mortality from breast cancer, and the most recent two cycles (in 2000 and in 2005) have shown that the effects on 15-year mortality are more than twice as big as the effects on 5-year mortality from breast cancer. Although it would eventually have become clear even without this worldwide collaboration that chemo-endocrine treatment did affect 5-year survival, the EBCTCG collaboration may well have accelerated the process, and may have been particularly helpful in assessing reliably the effect on 15-year survival. Chemo-endocrine treatment has been used increasingly widely since the early 1980s, and, partly as a results of this, breast cancer mortality rates have started to fall since 1990 in several developed countries. The 2005 and 2010 cycles will help answer the therapeutic questions of the 1990s, but the therapeutic questions today cannot be answered by large-scale randomised evidence with appropriately long-term follow-up until 2015 or 2020. The assessment of moderate differences in 15-year outcome is, unavoidably, a slow process – too slow, because patients need reliable answers now – but, over a period of decades, we do seem to be slowly winning.

References

[1] EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687–1717).

Monday, 31 October 2005

ESTRO Special session

2 ESTRO Award

The European Society for Therapeutic Radiology and Oncology (ESTRO) Klaas Breur Award – Head and neck cancers: a promising future for radiotherapy

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Radiotherapy plays a major role in the management of patients with head and neck cancer, either alone or more frequently associated to surgery and/or chemotherapy. Head and neck cancers have, for long, been a model to validate important concepts in the field of radiation oncology such as the importance of the overall treatment time, the benefit associated with chemo-radiotherapy and altered fractionated radiotherapy, the potential associated with hypoxic modifications, or intensity modulated radiotherapy etc. Radiotherapy is physically and dosimetrically targeted and biologically multi-targeted and there are strong suggestions that significant advances are taking place that may result in a relatively near future in marked improvements of its efficacy and tolerability, and may ultimately influence favourably cancer patients outcome.

There are 3 main areas in which optimisation of radiation therapy can provide a great potential of improvement, namely ballistics, imaging, and biology.

Regarding ballistics the limits are not reached and numerous approaches are being pursued including optimisation of the quality of the beam (protons), and of the delivery with intensity modulated radiotherapy, and image guided radiotherapy. These techniques should contribute to safely reduce the margins around the tumour (PTV), while allowing to deliver more dose within the target volume (GTV). These improvements have been parallel to the availability of more accurate multimodal and fusion imaging, along with the possibility to capture patient, organ and tumour motion. Moreover some of the new radiotherapy techniques may also allow to deliver a higher dose to the most active part of the tumour, as determined by functional imaging. This concept of "dose painting", introduced by Clifton Ling has a great potential, aiming to use biological tumour characteristics to be taken into account for adapting the irradiation. This includes CT-PET imaging using ^{18}FDG, ^{11}C-Methionin and other specific probes (FAZA, F-miso for hypoxia, proliferation, etc.), MR spectroscopy that can provide a real metabolic profile of the tumour, functional MRI and Doppler ultrasounds with contrast agents that can image microangiogenesis. Functional imaging may not only contribute to determine more precisely the ballistics of irradiation, but may also help in determining biological characteristics of the tumours that can drive the concomitant use of biological modifiers. In this field, a proof of principle has been obtained recently, showing that molecular targeting can be used successfully in combination with ionising radiation resulting in increased anti-tumour activity without increasing radiation toxicity. This was shown in a large randomised trial targeting EGFr and using a monoclonal antibody. Promising results have been obtained also when targeting hypoxia with hypoxic cytoxic agents, such as tirapazamine. Molecular targeting in combination with radiation therapy offers a great opportunity to improve the anti-tumour efficacy and/or to decrease the toxicity on normal tissues using selective radio-protectors.

In addition to these changes being progressively implemented in the practice of head and neck radiation oncology, there are also some more futuristic projects with a great potential such as the laser generated proton beam project and the use of monochromatic X-rays that can offer a ballistic advantage close to protons and also markedly and selectively increase the biological anti-tumour effect of the irradiation.

3 INVITED

Radiation oncology – the fusion of physics and biology

J.E. Tepper. *University of North Carolina School of Medicine, Dept of Radiation Oncology, USA*

Radiation oncology has historically been a field that has been dominated by technological advances with improvements in the evaluation of tumor extent, and treatment delivery approaches which have allowed radiation therapy to be delivered with less irradiation of uninvolved normal tissues and more accurate irradiation of tumor volumes. Radiation biology, although critical in understanding the effects of radiation and allowing a biological direction of clinical trials with altered fractionation schemes and radiation sensitizers, have not always had the improved knowledge translated into direct clinical application. Our definition of the biology of most tumors, until very recently, has been based on simple evaluations of the site of origin of the tumor and its histology based on H and E microscopic slides.

With the advances in our understanding of the biology of carcinogenesis and tumor progression, and improved knowledge of the molecular biology behind cellular response to radiation and other cancer therapeutics, we are now at a point where the opportunities for integration of biology into daily clinical practice is coming near. For example, polymorphisms in DNA repair enzymes may impact both the likelihood of developing cancer and the likelihood of responding to therapies that are directed at producing DNA injury. We will be able to define better those patients who are at high risk of tumor recurrence based on the biological characteristics of individual tumors. Although the anatomic TNM stage of the tumor will remain of great importance, it will be a less dominant factor than in the past.

As we improve our knowledge of the biology of cancer and the interaction of biology with therapeutic schemes, we must also continue to enhance the technical delivery of radiation. This includes improved diagnostic imaging, both physiological and anatomic and its integration with therapeutic technology, as well as improved radiation delivery approaches themselves. The integration of technology with biology will allow us to better determine what we should do for treatment of a given patient as well as improve markedly our ability to deliver that therapy accurately and with minimal normal tissue injury. Advances in radiation oncology will come from a fusion of biology and technology in the therapy of cancer.