Teaching Lectures

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Assessing the quality of life of cancer patients: Where are we now? A European perspective

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The concept of assessing systemmatically cancer patients' experience of their disease and treatment as an outcome measure in clinical trials in oncology has gained wide international acceptance. There is now a choice of so-called quality of life (QL) measures of proven reliability and validity available for this purpose. The application of these measures can generate clinically useful data but as yet the quality and volume of the published output from European studies does not adequately reflect the level of activity. This presentation will draw on the experience of the EORTC QL Study Group to identify common pitfalls in the design and conduct of QL studies in clinical trials and suggest how these might be overcome. Attention will be given to adequate definition of the research question which determines the choice of measurement tool. The requirements for obtaining good quality translations of questionnaire measures will be specified. The assessment schedule will be discussed with reference to the study question and the pragmatic issues in data collection with the aim of enhancing compliance in order to collect maximally informative data. Clear analysis plans for the QL data need to be specified in the protocol. A wealth of documentation is now available to support users of the EORTC instruments and training courses are increasingly available. Future prospects for the further development and clinical application of QL assessment will be summarised briefly.

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Ovarian cancer – Second-line chemotherapy: What are the options?

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Relapsed ovarian cancer remain an incurable condition but in recent years the number of drugs available to treat this situation has increased considerably. One of the most important management decisions concerns the timing of chemotherapy which remains an area of uncertainty. There is evidence that the longer the treatment-free interval, the more likely patients are to respond to chemotherapy but other factors such as tumour size, performance status and anaemia are also prognostic factors for response. One of the most difficult decisions is whether or not patients who have an asymptomatic rise in CA 125 without any evidence of disease on CT scanning or clinical examination, should be treated immediately. An MRC-EORTC study is currently addressing this issue of early versus late treatment in relapsed disease. Once a decision has been made to treat the patient then the relapse-free interval following platinum therapy is an important criteria for deciding which drug(s) to use. Generally, patients with an interval over 12 months should receive a platinum compound either alone or in combination and for patients who relapse within 12 months, single agents such as topotecan, anthracyclines, etoposide, altretamine, gemcitabine or paclitaxel, all give very similar response rates. This group of patients can also be treated with platinum-based combination therapies and higher response rates are achieved although at greater toxicity. Debulking surgery does not usually form part of the management of patients who have relapsed within 12 months although palliative surgery to remove solitary symptomatic masses is sometimes indicated. Patients who relapse late after first-line treatment are candidates for further surgery.

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Imaging in radiotherapy: An explosion of technology

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Rapid developments in technology have made it possible to image tumours and calculate dose distributions for radiotherapy in 3D. Using precise immobilisation and localisation of the tumour and complex beam configurations, conformal radiotherapy enables smaller volumes to be treated to higher radiation doses with a potential for cure. What are the pitfalls?

Definition of the planning target volume remains the most difficult step in the radiotherapy procedure. ICRU 62 (Supplement to ICRU 50) published in 1999 addresses recently published data on tumour margins, organ motion, set up variations and verification studies and proposes modified classifications to the target volume to accommodate these new data. Illustrations will be presented from various tumour sites.

MRI gives excellent soft tissue evaluation of many tumours and multimodality image registration techniques are being developed to match different imaging data sets. These accurately shaped volumes can now be treated using beam intensity modulated radiotherapy with customised compensators or multileaf collimators (MLC) using static fields or dynamic movement of the MLC. Organ motion such as respiration and cardiac pulsation present a problem for such precisely controlled irradiation and remaining challenges will be discussed.

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Inhibitors of mitogenic signal transduction as novel antitumor agents: Prospects and limitations

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The majority of compounds which are presently employed in tumour chemotherapy have been used since three decades and more. In view of this situation it is not surprising that the advances in tumour chemotherapy have remained modest and are restricted to a few selected malignancies like M. Hodgkin or testicular cancer. This is in marked contrast to the enormous progress obtained in our understanding of the molecular mechanisms regulating normal and maligant growth highlighted by the discoveries of oncogenes, tumour suppressor genes and their biological functions. These studies revealed that malignant growth can be adequately described as a dysregulation of cellular signalling mechanisms. The identification of the signalling mechanisms regulating cellular proliferation, apoptotic cell death, angiogenesis etc. has lead to a plethora of novel targets for pharmacological intervention and a flood of new potentially powerful antitumour agents. The lecture will present an overview of signal transduction inhibitors which appear to be promising agents in toumour chemotherapy and their mechanisms of action, focusing on those for which data from clinical trials are available. Their prospective usefulness as well as their limitations will be discussed.

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Regional treatment – Progress and limitations

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When the tumour spreading is limited to a body region, it is possible to deliver drugs regionally with the aim of increasing therapeutic efficacy. Selected clinical conditions include: inextirpable limb tumours, metastatic localisations in single organ or region (i.e. liver metastases, malignant ascitis). Several techniques can be used: intra-arterial infusion (with drugs allowing a first passage effect), intra-peritoneal infusion, stop-flow perfusion (blocking the aortal and veinacaval flow), Isolated limb perfusion (ILP) and isolated hepatic perfusion (IHP) (giving the highest area under the curve).

The highest rate of response were obtained in ILP and IHP. In ILP with a combination of TNFalpha and chemotherapy for inextirpable soft tissue sarcomas, limb salvage from amputation was 80%. 70 to 80% complete responses were reported in in-transit melanoma metastases of the limbs. Objective responses have been reported in liver metastases (colon carcinoma, ocular melanoma), using IHP or intra-hepatic artery infusion. Stop-flow treatment of advanced ovarian carcinoma with malignant ascitis, advanced pancreas carcinoma, and pelvic tumours are currently evaluated.

Achievements of local tumour control may interfere with life threatening progression of cancer but the limitation of a regional treatment is that the treatment intensity is confined to the region. In absence of objective response, pain alleviation in pancreas and pelvic cancer could improve the quality of life. The isolated limb perfusion with TNFalpha and melphalan is a model whereby a double targeting is obtained: TNFalpha is destroying the tumour vascularisation and the chemotherapy the tumour cells themselves.

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Determining and comparing the costs of treatments

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This lecture sets out the basic principles of how to determine the costs of medical treatments and illustrates the proper use of such cost calculations.

Calculation of the costs of a medical treatment or other intervention begins with determining the perspective from which the costs shall be assessed. What is to be included as costs, and particularly the appropriate unit prices, is determined by the perspective chosen, which may be that of society at large, the sickness insurance system, the hospitals or the patients. The next step is to identify all the different types of resources involved in each of the compared treatments. Such resources may be the time and knowledge of physicians and other health care personnel, medications used, examinations and tests performed, days spent in hospital, etc.

When the relevant resources have been identified, the next steps are to assess how much of each is used per patient, and to find a proper unit price for each type of resource. Finding appropriate unit prices, for instance for a CT scan, is a major problem for cost assessments, because there is usually no market price. Further, the accounting systems used by most hospitals do not allow one to determine the costs of a specific procedure performed on a particular patient. Usually, the economic analysts will have to content themselves with approximative estimates of the proper unit prices. The final step is to determine the average total cost per patient by multiplying the average quantity used of each resource by its unit price and summing over these products.

The cost of a medical treatment must be related to its outcome in terms of improvement of the patients' health in order to be interpreted meaningfully. The principal purpose of economic evaluations of treatment options in health care is to carry out so-called incremental analyses, in which the costs and outcomes of each of the options are simultaneously considered. Ultimately, an economic evaluation will result in an estimate of the change in average costs that will accompany the change in expected outcome by shifting from one treatment option to the other.

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Clinical applications of photodynamic therapy with second line photosensitizer

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Over the last years major advances have been made in the clinical application of photodynamic therapy (PDT). The more powerful second generation photosensitizers, suitable light sources and applicators of light makes this type of treatment more useful for the clinician. Of the second generation photosensitizers (Foscan, BPD, 5-ALA, Npe6, SnET2 and texaphyrin), the different absorption peaks and pharmacokinetic profiles all lead to specific indications. The basic mechanism of action is generally the same and based on vascular occlusion at illumination. Selectivity of the drug for tumour tissue has not proved to be very high. In general local light application is given hours to days after injection of the photosensitizer. Oxygen is required for the type II reaction, which leads to primarily vessel damage rendering the tumour hypoxic. To lesser amount, direct cell kill occurs.

Therefore, application of PDT for advanced tumours is limited because of hypoxic areas in the tumour occurs and light cannot always penetrate deeply in large volume tumours. Clinical applications are especially the early stage tumours in head and neck, Barrets oesophagus, early stage oesophageal and bronchial cancers, skin tumours (multipel basic cell carcinomas), bladder cancer and brain tumours.

A new field of application of PDT is as an adjunct to surgical resection after gross tumour resection (e.g. mesothelioma or abdominal surgical resections). Non oncologic applications of PDT are treatment of atherosclerosis, rheumatoid artritis and macular, ocular degeneration.

[1] Radiotherapy and Oncology 48 (1998) 233–245.