27 INVITED

Radiotherapy view

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Background: The majority of bladder cancers are superficial tumors (Ta, T1, Tis) which can effectively be controlled by TUR-BT in most cases. About 20% of bladder cancers, however, invade the muscle or spread beyond the bladder wall (T2−4); for these tumors, cystectomy has been used as standard treatment in most European countries since decades. Radiotherapy has been considered as treatment option only for inoperable tumors or as pallitive therapy. However, improvements in radiation oncology over the past 20 years (including combined modality approach with radiochemotherapy, 3D-treatment planning) have increased the efficacy and decreased the risk of side effects of curative radiotherapy. Moreover, radiotherapy offers the chance of organ- and function-preservation in the majority of patients. The objective is to give an evidenced-based overview over current treatment results of radiotherapy with special emphasis on treatment of elderly patients.
Results: There are no randomized trials comparing a multimodal bladder-sparing approach (TUR-BT plus radiochemotherapy plus salvage-cystectomy) with radical cystectomy. Retrospective and older single center series suggested some advantage for cytectomy; these data, however, have limited value due to selection bias. A variety of prospective phase-II-studies with radiochemotherapy have demonstrated highly encouraging results which are, with regard to survival, at least comparable to radical cystectomy. All series have reported a very low risk of severe side effects and a bladder preservation rate of 70−80% in long-term survivors. This holds also true for elderly patients.
Conclusions: TUR-BT plus radiochemotherapy is an evidence-based effective treatment for locally advanced bladder cancer (cT2−4) with the chance of bladder preservation in more than 70%. It is surely the treatment option of first choice in elderly patients and in patients with contraindications to surgery and the only curative approach in non-radically resectable tumors.

Special Session (Mon, 21 Sep, 14:00−15:00)
DNA repair of radiation damage

28 INVITED

What is new in DNA repair of radiation damage?

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The clustered nature of energy deposition events generated by ionizing radiation causes damage to both strands of the DNA molecule and leads to the formation of double strand breaks (DSBs) and other complex lesions. Damage to both strands deprives the cell of the immediate source of template normally used for the restoration of the DNA molecule after the induction of damage affecting only one strand. As a result, the DSB is a particularly severe form of damage whose repair is challenging for the cell and whose misrepair the source of events leading to genomic instability and cell death. Despite their severity, cells of higher eukaryotes display an astonishing capacity to remove DSBs from their genome. It is now well documented that DSBs are removed from the genomes of different types of organisms using two conceptually different repair pathways. The first repair pathway utilizes homology available elsewhere in the genome to restore structural integrity and sequence fidelity in the DNA molecule. This mechanism, termed homologous recombination repair (HRR), operates in a mostly error-free manner, is relatively complex and therefore slow, and is optimized to function after DNA replication using the sister chromatid as a source of homology. The second repair pathway is optimized to rejoin DSBs without any homology requirement, in a cell cycle independent manner and to restore structural integrity but no sequence fidelity in the molecule. This mechanism, termed non homologous end joining (NHEJ), is capable of quickly removing DSBs from the genome and in its classical form utilizes as central components Ku, DNA-PKcs, DNA Ligase IV, XRCC4 and XLF/Cernunnos. It is therefore also referred to as D-NHEJ to indicate its dependence on DNA-PK. Recent advances regarding the function of these DSB repair pathways will be reviewed. In addition, the question of pathway selection and issues raised by the necessity of selecting among dissimilar repair processes will be addressed. Furthermore, work carried out in our laboratory and elsewhere showing that when D-NHEJ is chemically or genetically compromised cells do not shunt DSBs to HRR but use instead another form of NHEJ operating as a backup (B-NHEJ) will be presented and the molecular make up of this alternative repair pathway briefly outlined. The possible involvement of B-NHEJ in carcinogenesis and cell death will be addressed. Finally, the relevance of information on DSB repair in the manipulation of the cellular response to DNA damage will be outlined and its importance in developing novel strategies for improving the treatment of cancer briefly mentioned.
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29 INVITED

How can we utilise DNA repair assays in prediction of radiation response?

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The radiotherapy dose delivered to a patient is selected to maximise tumour control whilst minimising late normal tissue complications. Patients display a range of tumour and normal tissue responses due to intrinsic cell radiosensitivity. In the 1980 s and 1990 s attempts were made to predict normal tissue responses using the clonogenic assay of reproductive cell death, with a view to either individualising dose prescriptions or removing radiosensitive individuals from a patient cohort in order to dose escalate the remainder.
The clonogenic assay is unfortunately too time-consuming to be of practical use prior to radiotherapy and therefore attention turned to the potential use of DNA repair assays, including the Comet assay and pulsed-field gel electrophoresis (PFGE) as more rapid surrogate endpoints. These also had the advantage that double strand breaks (DSB) are responsible for the major biological responses to radiotherapy. Therefore, not only cell death effects could be studied but also effects of altered gene expression, which regulates cellular differentiation and collagen disposition, important in the development of late radiation effects. Results of the PFGE assay and clonogenic assay were found to correlate in fibroblasts, and results of the PFGE assay correlated with fibrosis severity in a cohort of breast cancer patients. Unfortunately, these results were not confirmed in a validation study of patients who had been treated using a more modern radiotherapy technique with less inhomogeneous dose distributions, and with too much assay noise and criticism of the 150 Gy doses of radiation required, this assay was not taken forward to a prospective study.
The Comet assay is more sensitive and needs only small numbers of cells, but is also *in vitro* based and requires a single cell suspension. A criticism of this assay is that not only DSB but also chromatin structure and other factors influence comet formation.
The recent development of the γH2AX assay, which is sensitive in the fractionated radiotherapy treatment dose range, and which can be used to study *in vivo* DNA damage and repair, has resulted in renewed interest in the use of DNA repair assays in prediction of radiation response. This method is based on detection of serine 139 phosphorylation in the histone H2A variant, H2AX, at DSB sites. Discrete nuclear foci are generated which can be detected by immunofluorescence microscopy. The assay has been used to detect DSB in within-field skin biopsies from prostate radiotherapy patients and to measure DNA repair in peripheral blood lymphocytes from patients undergoing CT scans.
Genotyping of DNA repair gene single nucleotide polymorphisms (SNPs) in germline DNA is also being explored as a possible predictive tool of normal tissue response, as is immunohistochemical expression of DNA repair proteins for tumour response to radiotherapy.
Other DNA repair assays now available include the I-SceI homologous recombination assay, the *in vitro* non-homologous end-joining assay, and live cell imaging techniques of DNA repair protein recruitment to sites of focussed DNA damage. These assays shall be discussed in terms of their contribution to our understanding of the DNA damage response.

Special Session (Mon, 21 Sep, 14:00−15:00)
Cancer treatment in emerging countries

30 INVITED

Facing increasing costs of cancer care: Polish experience

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The incidence of cancer is increasing in Poland (approximately 140 000 newly diagnosed patients in 2006) and prognosis of patients with the majority of malignant diseases is still unacceptable. The anti-cancer expenditures increase, but in a rate less than the burden of cancer in Poland. Additional resources are necessary, but it is also imperative to use available health resources in an optimal way to achieve the best possible effects. This is particularly important in a middle-income country with limited overall health service spending (6% of gross domestic product) and low expenditure in oncology (5% of all medical costs). The key areas of anti-cancer activity in Poland include society-oriented health education,

collection and analysis of registry data, primary and secondary prevention, promotion and implementation of optimal practice guidelines, improvement of treatment access as well as cancer research. These activities are covered by the National Anticancer Program established in 2005 in line with the World Health Organization recommendation. Investing in cancer screening programs will pay the highest dividends, since prevention is the most cost-effective way to minimize burden of cancer. Unfortunately, less than one-third of the recommended numbers of screenings (breast, cervical and colorectal cancer) take place in Poland each year. Inequalities in the access to treatment modalities (particularly, new anti-cancer drugs) are also of concern in Poland. Escalating costs of anti-cancer drugs makes allocation of limited resources particularly important. Actions to improve the drug access in Poland include the use of health technology assessments and separate funding of some most expensive drugs from a central reimbursement system. All innovative therapies are monitored with respect to appropriateness of indications and treatment conduct. Our aim is to follow the outcomes of new treatments more carefully and promote the most effective ones. Another area of interest is to employ more flexible pricing schemes in Poland – i.e, conditional reimbursement and cost sharing. Clinicians with specialist knowledge are motivated to have more substantial input into the process of new treatments assessment considering good-quality and evidence-based clinical guidelines with the aim to reimburse new agents in patients who are likely to benefit and in whom particular drugs are recommended. Coordination of regulatory institution and appraisal agency activities has to be improved in Poland – the former is concerned of safety and efficacy, whereas the latter pays attention mainly to "real-life" outcomes. The increasing complexity of cancer care will progressively strain the medical system. It is important to reduce inabilities and disparities with additional resources, but modification of structural conditions is essential.

31 INVITED

Management of breast cancer in limited-resource countries

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Background: Guidelines for breast health care (early detection, diagnosis and treatment) that were developed in high resource countries cannot be directly applied in limited resource countries (LMC), because these guidelines do not consider real world resource constraints, nor do they prioritize which resources are most critically needed in specific countries for care to be most effectively provided. A key determinant of breast cancer outcome in any population including those from low- and middle income countries (LMCs) is the degree to which newly diagnosed cancers can be correctly treated in a timely fashion using multimodality cancer therapy that is properly selected and delivered. Panels of breast cancer experts and patient advocates met within the Breast Health Global Initiative to specifically develop consensus recommendations on how breast cancer can best be managed under the constraints of significantly limited resources.
Methods: Through a series of three Global Summits, the BHGI multidisciplinary panels of experts addressed the implementation of breast health care guidelines for early detection, diagnosis and treatment in LMCs. The panels reviewed the previously devised stratification tables, discussed core implementation issues related to breast treatment, and made relevant changes based on consensus opinion. Resource requirements were summarized as process checklists for (1) breast surgery, (2) radiation treatment and (3) systemic therapy. The needed resources for stage I, stage II, locally advanced and metastatic breast cancer were outlined. Process metrics were developed, based upon the priorities established in the guideline stratification.
Results: The ability to perform modified radical mastectomy (MRM) is the mainstay of locoregional treatment at the basic level of breast health care. The availability of radiation therapy allows for consideration of breast conserving therapy, post-mastectomy chest wall radiation, and for the palliation of painful or symptomatic metastases. The use of systemic therapy cytotoxic chemotherapy is effective in the treatment of all biologic subtypes of breast cancer, but is more resource intensive to provide. The provision of endocrine therapy requires relatively few specialized resources, but optimally requires knowledge of hormone receptor status to assure treatment of patients most likely to benefit. HER2-targeted therapy is very effective in tumors that overexpress the HER2/neu oncogene, but cost largely prevents the use of this treatment in LMCs.
Conclusions: Thoughtfully applied resource allocation for breast cancer treatment can improve care delivery in LMCs. The incremental, step-by-step allocation of resources can help address economic disparities across populations and provides a means for better ensuring equity in access to care. The use of checklists and allocation tables is a pragmatic approach, which recognizes that the ultimate goal of every health care system is to offer optimal care to all patients. The use of process metrics can facilitating the development of multidisciplinary, integrated, fiscally responsible, continuously improving, and flexible approaches to the global enhancement of breast cancer treatment.

Special Session (Mon, 21 Sep, 14:00−15:00)
Assessment and measurement in cancer care

32 INVITED

Developing cancer rehabilitation using appropriate assessment of need

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Cancer rehabilitation aims to maximise a person's ability to function, to promote their independence and to help them adapt to their condition (National Institute for Clinical Excellence NICE 2004).
Dietz (1981) described how rehabilitation is appropriate to all stages of the cancer trajectory, in that it can be preventative, restorative, supportive or palliative.
This presentation will explore a selection of the tools available to assess, plan and evaluate the rehabilitation needs of people affected by cancer.
The tools presented will all be adaptable for multi-professional use.
Case studies from practice at the Royal Marsden NHS Foundation Trust will be used to demonstrate application in a variety of settings.
Canadian Occupational Performance Measure (COPM) is a client centred, individualised measure designed by occupational therapists. It aims to detect change in occupational performance as perceived by the client over time. It is based around a semi-structured interview and designed as an outcome measure as it has a structured scoring method (Baptiste et al 1993).
Functional Independence Measure (FIM) is an 18-item global measure of disability, scored on 7 ordinal levels from complete independence to total assistance. Function, based on observation, is assessed by clinicians before and after any rehabilitation intervention (UDSR 1997).
Distress Thermometer (DT) is a single item tool designed to measure psychologic distress that can be completed by individuals in any setting. It has a simple numerical scale and an accompanying problem list to assist people in identifying what has caused them distress in the last week. A scoring system facilitates the professional to suggest an appropriate action plan (American Cancer Society 2004, Jacobsen et al 2005).

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33 INVITED

Using evidence to measure complex symptoms

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The management of complex symptoms is reliant on an ability to sensitively measure patient-reported experiences of health-related problems. To date, measures available to inform the efficacy of nursing and supportive care (NSC) interventions targeting complex symptoms, lack sensitivity. As a result, studies often fail to demonstrate therapeutic benefit even when strong anecdotal evidence to the contrary is present. This paper reviews several key outcome measures used in NSC randomised controlled trails and highlights their limitations to inform developments in evidence-based management of complex symptoms. Evidence to inform essential components of NSC interventions are considered and questions raised about how this evidence can contribute to improved measurement of complex, cancer-related symptoms.