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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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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,