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Penile Cancer − Chemotherapy

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Penile cancer is a rare disease and accounts for only about 0.5% of all malignancies. Advanced (T3/4) or metastatic disease is even rarer, comprising only 5% of patients in Europe and up to 13% in Brazil.
The role of chemotherapy in the treatment of penile cancer is limited. For patients with fixed or relapsed inguinal nodes upfront combination chemotherapy followed by surgery is recommended. In the adjuvant setting chemotherapy should be considered for patients with pN2/3 disease, although supporting data is scarce. Combination chemotherapy can provide palliation in the case of metastatic disease or relapse.
There are only very small retrospective series and very rare prospetive trials with multiple chemotherapy regimens and partly conflicting results. Since the late 1980-ies the following compounds have been used as single agents, but mostly in combination: methotrexate, bleomycin, cisplatin, 5-fluorouracil (5-FU), vinblastin. More recently the taxanes, irinotecan and ifosfamide have been added to the chemotherapeutic armamentarium. Cisplatin combination chemotherapy is active in penile cancer with response rates of about 20%. The highest response rate of 32% was reported in one of the larger series from the South West Oncology Group with one oft he regimens of the 1990ies (methotrexate, bleomycin, cisplatin). However, toxicity was very high with five treatment related deaths. Cisplatin has become the basis of chemotherapy combinations in more recent series, mostly combined with 5-FU, which is the recommended combination in the European guidelines. The EORTC conducted one of the rare prospective trials and explored the efficacy and safety of cisplatin and irinotecan (Theodore et al, Ann Oncol 2008). The response rate was 31%, including two complete pathologic responses (pCR). Neoadjuvant paclitaxel, ifosfamide, and cisplatin showed an objective response rate of 50%, including three pCR, and acceptable toxicity in a 30 patient prospective trial (Pagliaro et al, J Clin Oncol 2010). The inclusion of the taxanes and contemporary chemotherapy support add to the efficacy of chemotherapy and the reduction of toxicity in the treatment of locally advanced and metastatic penile cancer.

Special Session (Sat, 24 Sep, 14:15−15:15) **Immune System and Tumour Response to Radiotherapy**

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Role of T-Lymphocytes for Tumour Response to Radiotherapy

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Over the past ten years we have developed a clinical translational program based on the rationale of immunizing patients against their own tumour by concomitantly: 1) removing existing “breaks“ in their immune system and 2) harnessing local ionizing radiation (IR) to induce physical and biological perturbations at the irradiated tumour site, to achieve the successful conversion of the original tumour into an immunogenic hub (Formenti, Lancet Oncology 2009). Preclinical investigations have shed some light on the specific role of T cells in these processes. For instance, in the 4T1 syngeneic murine model of metastatic breast cancer targeting regulatory receptors or cells (Treg) by anti-CTLA-4 and anti-CD25 antibodies, respectively, synergized with IR and reduced the number of metastases to the lung (an abscopal effect, defined as a significant growth inhibition of the tumour outside the irradiated field) in a CD8+ T cells dependent way. In the same model IR increased the migration of CD8 CXCR6 activated T cells to tumours. This effect was mediated by IR-enhanced secretion by cancer cells of CXCL16, a chemokine that binds to CXCR6 on Th1 and activated CD8 effector T cells. CXCR6-deficient mice showed reduced infiltration of tumours by activated CD8+ T cells and impaired tumour regression following treatment with local IR + CTLA-4 blockade.
Interestingly, an abscopal effect, occurred only in mice treated with the combination of 9H10 and fractionated radiotherapy, but not when a single dose of 20 Gy was administered ($P < 0.01$), as reflected by the frequency of CD8+ T cells showing tumour-specific IFN-gamma production.
The contribution of invariant natural killer T (iNKT) cells, a subset with unique regulatory functions, in the response to IR and CTLA-4 blockade was also studied. Growth of 4T1 primary tumours and lung metastases was compared in wild type (WT) and iNKT cells-deficient (iNKT−/−) mice. The response to IR+CTLA-4 blockade was markedly enhanced in the absence of iNKT cells: 50% of iNKT−/− compared to none of the WT mice had complete tumour regression, long-term survival, and resistance to a challenge with 4T1 cells.
Finally, intravital microscopy demonstrated that while both IR and CTLA-4 blockade given as monotherapy enhanced the motility of activated CD8 T cells infiltrating 4T1 tumours, IR with anti-CTLA-4 increased the arrest of T cells in contact with tumour cells. The latter required interaction of NKG2D on CD8+ T cells with its ligand retinoic acid early inducible-1 (Rae-1) on the tumour cells, which was up-regulated by IR. Blocking NKG2D-Rae-1 interactions increased markedly the motility of anti-CTLA-4 treated T cells within irradiated tumours inhibiting their contact with tumour cells, and abrogated immune-mediated tumour rejection, suggesting a critical role of radiation-induced NKG2D ligands for the antitumour effects of anti-CTLA-4 in the setting of a poorly immunogenic tumour.

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CD11b Cells Provide Resistance to Radiotherapy

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We are testing a new therapeutic paradigm based on the dual origin of tumour blood vessels: Angiogenesis, the sprouting of endothelial cells from nearby blood vessels, and vasculogenesis, the formation of blood vessels by circulating cells, primarily of bone marrow origin. We have shown that by killing the endothelial cells in and surrounding the tumour, local tumour irradiation abrogates local angiogenesis suggesting that the tumour has to rely on the vasculogenesis pathway for regrowth after irradiation. We have shown that local irradiation of human tumour xenografts in nude mice produces a large influx of bone marrow derived CD11b+ myelomonocytes into the tumours as they begin to regrow following irradiation. We demonostrate that inhibition of this influx using neutralizing antibodies against CD11b inhibits tumour recurrence. Thus the influx of CD11b+ monocytes promotes tumour recurrence after irradiation. The mechanism for this effect could be by their proangiogenic nature or they could be suppressing T-cell immunity by their nature as myeloid-derived suppressor cells (MDSC). The fact that these experiments were performed in T-cell deficient mice does not rule out the MDSC mechanism as we and others have demonstrated that there is residual anti-tumour immunity in nude mice. To distinguish the two mechanisms we also tested anti-Gr1 antibodies and showed no effect on tumour response to irradiation. As MDSC are Gr1+CD11b+ monocytes these data argue for the importance of the proangiogenic properties of Gr1− CD11b+ cells. We are testing other models including immunodeficient SCID mice to further interrogate the mechanism by which CD11b+ myelomonocytes promote tumour recurrence after irradiation.

Special Session (Sat, 24 Sep, 14:15−15:15) **Developments in Surgical Oncology**

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Improving the Diagnostic Pathway for Men With Prostate Cancer

Abstract not received

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Robotic Surgery − Opportunities and Issues for Nursing

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The operating theatre of the 21st century has become a hi-tech environment. Since the early days of laparoscopic surgery, there has been a continuous increase in the number of devices for surgical use thus, crowding of the operating theatre.
Robotic surgery is quickly replacing conventional surgery in several surgical specialties and is not only heralded as the new revolution, but is one of the most talked about subjects in surgery today. Such advances have facilitated significant improvements in the management of the surgical patient effectively cancer patients, minimising open surgical resections.
Results have shown that robotic procedures reduce recovery times in addition to a shorter hospital stay, reduced pain, reduced tissue damage, and scarring. This change bears a significant impact on the clinical practice of surgeons, surgical trainees and operating theatre practitioners.
In September 2000 the da Vinci Robotic System, the first of its kind to be installed in the UK, was introduced to Imperial College St Mary’s Hospital London. The role of the robotics nurse specialist was developed to create

a myriad of clinical responsibilities to the entire surgical team to promote positive patient outcomes.
This presentation will describe and discuss opportunities and issues for nurses who are new to, about to become involved with, or, who are already involved with robotic surgery; ***from handmaiden to right hand.***

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Health-Related Quality of Life as a Prognostic Factor in Patients With Oesophageal Cancer

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Background: Since treatment for oesophageal cancer is extensive and the long-term prognosis is poor, tools that can help predict the prognosis are warranted. The use of measures of health-related quality of life (HRQL) are becoming increasingly more common in clinical research, and accumulating evidence suggests that HRQL data can predict survival in oesophageal cancer patients.
Materials and Methods: The literature as available on PubMed was reviewed on this topic. Several cohort studies have been performed, some of which have been of population-based design. Results from randomised clinical trials with HRQL as a secondary outcome were reviewed also. The assessment of HRQL has mainly been based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) together with the oesophageal-specific module (QLQ-OES18).
Results: Based on the available literature, where adjustment for potential confounding factors has been performed, poor global quality of life, poor physical and role function, fatigue and appetite loss before treatment appear to independently predict a worse chance of survival. HRQL measured after treatment may also be of prognostic value. When measured 3−6 months after oesophageal cancer surgery, poor global quality of life, physical function and social function and symptoms of fatigue, pain, dyspnoea, appetite loss, dysphagia and odynophagia are associated with shorter survival. Improvement in physical function within 6 months of surgery has been found to be associated with a better chance of survival while increased pain and fatigue is associated with worse survival.
Conclusions: Measures of HRQL might be of use in predicting survival in patients with oesophageal cancer. HRQL can be used in clinical practice to direct the need for investigations to detect recurrent disease, and in the planning of follow-up, supportive care and palliative treatments. However, more research is needed to clarify the role of HRQL as a prognostic tool in the clinical management of oesophageal cancer patients.

Special Session (Sat, 24 Sep, 14:15−15:15)
Late Toxicity Treatment of Head and Neck Cancer

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Biological Insights

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Despite relatively high survival rates, the quality of life of head and neck patients is severely compromised because of radiation-induced impairment of salivary gland function and consequential xerostomia (dry mouth syndrome). Although is some patients a recovery can be seen even up to 5 years after irradiation, mostly the damage is permanent. Similar late regeneration of the salivary glands has been show in rats after fractionated irradiation. From these preclinical experiments radiation-induced hyposalivation has been described in 4 distinct phases. The first phase (0−10 days) was characterised by a rapid decline in flow rate without changes in amylase secretion or acinar cell number. The second phase (10−60 days) consists of a decrease in amylase secretion and is paralleled by acinar cell loss. Flow rate, amylase secretion and acinar cell numbers do not change in the third phase (60–120 days). The fourth phase (120–240 days) is determined by a further deterioration of gland function but an increase in acinar cell number, albeit with poor tissue morphology. The most primitive tissue stem cells, residing in the excretory duct seem to be responsible for the late regeneration of the tissue. Indeed, the maintenance and repair of the tissue integrity are the primary roles of the tissue stem cell. Stimulation of stem/progenitors before or after irradiation with e.g. pilocarpine of KGF, results in enhanced regeneration which however does not always lasts. Therefore, for the normal tissue it is of eminent importance to spare the tissue stem cells. Recently, it became apparent that the tissues stem cells may not be evenly distributed over the tissue. Irradiation of a critical 7 volume % part of the parotid glands, suggested to contain the tissues stem cells, indeed resulted in more than a proportional damage as shown by the reduced saliva production, whereas the non-centrally orientated volume induced a lower than proportional level of damage. Next to the tissue stem cells, also the vasculature plays a prominent role in late tissue damage. Together with extensive fibrosis, prominent telangiectasia can be observed in the salivary glands late after irradiation. However, mobilisation of bone marrow derived mesenchymal cells and endothelial progenitor cells have been shown to be able to prevent late vascular damage in the mouse salivary gland. In conclusion, the tissue stem cells and the vasculature play a major role in late salivary gland damage. Here specific sparing of high stem cell density regions together with enhanced circulating endothelial progenitor cells may yield an enhanced recovery after irradiation and improved salivary gland function.

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Late Functional Outcome in Chemo-Radiation

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The last decade, major progress has been made in the treatment of head and neck squamous cell carcinoma (HNSCC). There is growing evidence that more aggressive treatment regimens, either the delivery of radiotherapy with concomitant chemotherapy or altered fractionation schedules, improve tumour control and survival. However, these new treatment regimens have come to the expense of radiation-induced side effects (RISD), such as swallowing dysfunction and xerostomia. As quality of life is particularly affected by RISD, prevention of this side effect may improve the therapeutic ratio of treatment for HNSCC. One of the ways to prevent RISD is to reduce the dose to the anatomical structures involved in swallowing, i.e. the swallowing organs at risk (SWOARs) and salivary glands.
At the department of Radiation Oncology of the University Medical Center, all patients with head and neck cancer undergoing curative radiotherapy are subjected to standard follow up program in which acute and late toxicity is prospectively and systematically assessed at fixed time points during and after radiotherapy. Currently, more than 800 patients have been entered in this program, which enables studies on the relationship between radiation dose distributions in several organs at risk (OARs) and late toxicity.
In our prospective cohort, we found that xerostomia is the most frequently reported grade $\geqslant$2 RSID. Since the introduction of IMRT, the prevalence of this side effect has been reduced significantly as compared to 3D-CRT without sparing of the parotid glands. Recent results of our preclinical studies indicate that further improvement may be achieved by specifically sparing certain sub volumes within the parotid glands.
Another important late side effect is swallowing dysfunction, which has a major impact on patient-rated quality of life. The results of our prospective study showed that the dose in specific anatomical structures, such as the dose to the pharyngeal constrictor muscles and the supraglottic area are the most important factors for late swallowing dysfunction. In addition, swallowing dysfunction more frequently occur among patients treated with chemoradiation. In silico planning comparative studies indicate that sparing these SWOARs may result in a reduction of the risk of this side effect. The first results of a prospective phase II study on swallowing-sparing IMRT look promising in this regard. These results will be presented.
Conclusion: Parotid sparing IMRT significantly reduces the risk on xerostomia. Further improvement may be expected from sparing specific sub volumes of the parotid glands and possibly by proton radiotherapy. Swallowing sparing IMRT is expected to result in a significant reduction of swallowing dysfunction after curative (chemo) radiation.

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Late Functional Outcome Surgery

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Today's main guidelines for treatment in HNSCC are still based on phase III-trials and comprehensive metaanalysis with excess of radiation or chemo radiation at the expense of surgical trials. As stated by Higgens and Wang (Higgens 2008), clinical recommendations for HNSCC treatment based on evidence are difficult due this disproportion of surgical and non-surgical trials. This conflict is triggered by the fact that instruments for evaluating best surgical practice are different from methodological standards in non surgical phase-II or -III trials (this is nicely considered by Higgens 2008). Late functional outcome after surgery is becoming more evident since late functional outcome after multimodality treatment has been augmented as issue in comparison of best treatment in head and neck squamous cell carcinoma (HNSCC). To address this problem, Lefebvre and Ang