Results: Single treatments with either anti-PD-1 checkpoint-blocking or CD133-specific T cell-recruiting antibodies had only very little effect on tumor growth. Hypofractionated tumor irradiation alone delayed tumor growth more strongly, but also only transiently for about 2 weeks. Hypofractionated tumor irradiation induced tumor-specific effector T cells. In accordance with this, the double combination of local radiotherapy and anti-PD-1 antibody caused long-lasting tumor regressions including some complete cures, even in mice with large melanomas. Moreover, the cured mice remained immune to subsequent rechallenge with rather high doses of either $CD133^+$ or $CD133^-$ B16 melanoma cells. Noteworthy effects were also observed upon administration of the bispecific T cell-recruiting antibody into mice with irradiated tumors. The underlying mechanisms of these observations will be presented at the meeting.
Conclusions: The study suggests that the evaluation of potential synergistic radiotherapy/immunotherapy combinations in immunocompetent mouse tumor models can provide crucial information for clinical trial planning.

Award Lecture: Breur Award Lecture

SP-0488
Radiation Oncology and technological innovation: a fish desperately looking for a bicycle?

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High-tech solutions desperately looking for problems, or are we really making a difference?
"Modern radiation oncology is a well-established, cost-effective and essential component in the curative and palliative treatment of malignancy." A statement no one can argue with. The challenge of individualized treatment optimization continuously drives research and technology, yet we should be careful not to get trapped in the "Cargo Cult Science" as described by Richard Feynman. In this lecture, the author - coming from a radiotherapy department with in its banner the vision: "to offer the optimal and most efficient radiation therapy tailored to the individual patient, through development and clinical implementation of novel irradiation techniques" - takes a critical view on new technologies in radiation oncology. New developments are more likely to be adopted if they improve the workflow, and if the benefits are more favourable, or at least equal to current care. However, sometimes it seems as if we are in a blind gallop towards increasingly more precise means of tumour localization and irradiation, the perception being that it is largely driven by vendors rather than the care takers' or patients' needs. If development moves too fast, the focus might be too strong on the innovation itself and less on the (safe) implementation. Industry funded research doesn't help much, in that less favourable results do not always end up being published, hence inducing a strong bias towards a perception that improved treatment delivery requires high-tech solutions; whereas sometimes common sense might yield equivalent clinical results. Scientific and technological progress comes at a significant cost, and many concerns exist regarding the value of that progress. Within the current state of the economy, health care politicians face the difficult challenge to allow progress through efficacy and driven by outcomes. What's even worse is the danger that too much focus on sophisticated expensive technology may create a double layer health care system where not all patients have access to the best of care. In the end what counts is the result, not how we got there. Does this mean we have to refrain from innovation? Certainly not. Indeed, looking back at the technological progress that has been realized the last decades (perhaps "century" is more apt), this evolution has been translated successfully into clinical improvements both in patient cure as well as quality of life (with recent developments such as IMRT, IGRT, BCRT, IGBT, SBRT, IMPT, etc, as a proof of concept). In conclusion, it is safe to state that many good technological solutions are being developed as we speak, the challenge is to introduce these innovations adapted to the radiotherapy requirements (the end-users) … not the other way around.

Symposium with Proffered Papers: HPV and cancer and radiotherapy (H&N, cervix, vulva, anal)

SP-0489
HPV-transformation in the cervix and at non-cervical sites

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Human papillomavirus (HPV) infections are an essential cause for virtually all carcinomas of the uterine cervix and subsets of other anogenital, oropharyngeal and laryngeal tumors. The HPV aetiological contribution differs in each anatomical location reflecting differences in natural history and viral tissue tropism. Up to 99,9% of cervical, 80% of anal and 30% of vulvar cancers have been defined as HPV DNA positive by epidemiological studies. In the head-and-neck (H&N) region, HPV DNA positivity was detected in up to 50% of oropharyngeal (in Central Europe) and 35% of laryngeal cancers. However, recent studies on H&N cancers (specifically oropharyngeal cancer/cancer of the tonsil) have demonstrated that the presence of HPV DNA *per se* in invasive tumor tissues is insufficient proof for viral causality and could result in misclassification of malignant lesions and consequently, mistreatment of cancer patients. In addition, several studies have reported a better response to radiotherapy of HPV-driven oropharyngeal carcinomas, but not non-HPV-driven ones. Therefore, defining HPV-driven tumors by measuring markers of HPV-transformation in addition to HPV DNA, is crucial. Cervical squamous cell carcinoma (CSCC) is the best-understood model for HPV-transformation, and up to 99% of HPV DNA positive CSSC are also HPV-driven. In addition to HPV DNA presence, CSCC is characterized by: (i) at least 1 viral genome copy present in each tumor cell (viral load), (ii) expression of viral oncogenes E6 and E7 (HPV RNA), and (iii) alteration of steady state levels of cellular proteins, most consistently up-regulation of $p16^{INK4a}$. Outside of the cervix, this proof-of-principle marker combinations have been, to various extents, demonstrated for the cancer of the oropharynx, larynx, vulva and anus, with HPV16 being a leading transforming agent. In Central

Europe approximated fraction of HPV-driven oropharyngeal cancers is 25%, and laryngeal cancers only 5%, versus 50% and 35% suggested by HPV DNA studies for these anatomical sites, respectively. The use/usefulness of specific markers and marker combinations to define an HPV-driven tumor will be discussed.

SP-0490

Role of HPV status on Radiotherapy outcome in the various tumour entities.

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The recent understanding of mechanisms of HPV-induced carcinogenesis has lead to the development of prophylactic vaccines, however radiotherapy still remains a major therapy in HPV-related cancer and despite concurrent chemotherapy, the outcome remains suboptimal. Therefore, improving the radiotherapeutic index remains an important challenge as well as defining predictive assays for treatment outcome of HPV-related tumours. Elucidating the influence of the HPV virus on tumour radiosensitivity is of major interest. There is several lines of evidence showing that head and neck HPV-positive tumours have better outcome compared to non HPV related tumours and given the role of HPV oncoproteins on tumor immunity, it is possible that the feature of immune and microenvironmental factors during radiation response could be specific to HPV related tumors. Genetic feature of HPV+ cervical cancer has also been investigated and 3q gain has been shown to be particularly frequent in cervical cancers infected with the HPV16 virus type (84%) as well as in oropharyngeal and lung cancers. Other cancers such as anal and penile cancers are caused by or at least are associated with HPV infection. HPV-associated malignancies have common molecular feature, however specific response can also be expected and interfere with response to radiotherapy such as the contribution of organ-specific microbiota. In any case, investigating radiation response in this various type of cancer would help to decipher the role of HPV in radiation sensitivity and assess whether HPV+ cancer cells are intrinsically more sensitive to radiotherapy; or if HPV+ tumors release upon radiotherapy immunogenic viral proteins that promote tumor clearance and may prevent recurrence.This difference may allow for different combination of treatment strategies to be developed.

SP-0491

Clinical data (H&N, cervix, vulva, anal)

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Approximately 5% of all cancers worldwide are considered attributable to Human papillomavirus (HPV) and as such HPV associated cancers constitute a significant global disease burden. A causal relationship between HPV and cervical cancer was established almost 40 years ago and HPV is necessary for the development of cervical cancers, of which more than 99% harbour virus. Detection rates of HPV at other ano-genital sites (vulva, vagina and anus) are somewhat lower (65-80%), and clinical data suggest that outcome at these sites differ significantly dependent on the HPV-status of the tumors, in a way that patients with HPV-positive tumors have better prognosis compared to HPV-negative patients.

In head and neck cancer (HNSCC), tobacco and alcohol were until recently considered to be the major risk factors for carcinogenesis. However, the putative role of HPV in HNSCC has been investigated since the 1980s, and at present sufficient molecular and pathological evidence exists to etiologically link HPV to a subset of HNSCCs. The strongest association with HPV is found in oropharynx cancer (OPC) where tumors of the tonsils are particularly associated with HPV infection, but high-risk HPV, predominantly HPV-16, has been found in HNSCC from all sites although with a significantly higher prevalence in OPC compared to tumors arising outside the oropharyngeal region (non-OPC).

Numerous clinical studies have demonstrated a highly significant impact of tumour HPV/p16-status on radiotherapy (RT) outcome in advanced OPC where the influence of tumor HPV/p16-status seems indisputable. These observations are believed to be caused in part by a higher sensitivity of HPV/p16-positive tumors to RT, combined with a different and more favourable risk factor profile (including less heavy tobacco history) and better general health status in the group of patients with HPV/p16-positive disease. Less is known about the influence of HPV/p16-status in non-OPC and clinical data published so far have reached different conclusions. Data based on a rather large cohort of patients with advanced larynx and hypopharynx cancer treated with primary (chemo)radiotherapy suggested that the prognostic impact of HPV/p16-status does not extend to tumors of non-oropharyngeal origin. The reasons for this apparent site-specific difference in the prognostic impact of HPV/p16-status in HNSCC remain unsolved and warrant further investigation.

Presently there is substantial variation in the treatment strategies considered for patients with head and neck cancer dependent of the HPV/p16-status of the tumors. Some clinical trials are investigating whether de-intensified treatment strategies could result in avoidance of excessive toxicity without compromising outcome for selected patients with “low-risk” HPV/p16-positive OPC. At the opposite end of the spectrum other trials are investigating whether additional intensification of treatment could be beneficial for patients with HPV/p16-negative HNSCC based on their observed poor outcome, in order to secure optimal and safe treatment for these patients also.

OC-0492

Estimation of HPV 16 and 18 subtypes, viral load and correlation with response to radio (chemo) therapy in cervical cancers

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Purpose/Objective: Etiologic role of Human Papilloma Virus (HPV) in cervical cancer is well established. Radio (chemo) therapy remains the mainstay of treatment. Response, relapses & overall outcome and correlation with HPV is not well known. With an aim to study this we undertook this study.

Materials and Methods: After Institutional Ethical clearance and obtaining written informed consent patients were invited to participate in this prospective observational study. Patients who were treated with radio (chemo) therapy for cervical cancer underwent quantitative estimation of HPV 16 and 18 viral load pre treatment, at treatment completion, 2 and 5 months post treatment on cervical biopsies/ brushings using polymerase chain reaction (PCR). The viral load were compiled, evaluated and correlated with standard clinical response evaluation.