OC-0486
Nodal failure after (chemo-)radiation and MRI guided adaptive BT in cervical cancer: a sub-analysis within EMBRACE
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Purpose/Objective: Advanced cervical cancer patients treated with (chemo-)radiation and MRI-guided adaptive brachytherapy (MR-IGABT) have high local control rates with acceptable treatment related morbidity. However, nodal recurrence is still a matter of concern. The aim of this study was to analyze the pattern of nodal failure in patients enrolled in the EMBRACE study (www.embracestudy.dk) and to explore potential predictive factors.

Materials and Methods: Eight hundred and fifty-seven patients were treated at least 12 months prior to analysis. A number of 410 patients were lymph node negative and 406 patients were lymph node positive at time of diagnosis. Lymphadenectomy or nodal debulking was allowed prior to (chemo-)radiation. All affected lymph nodes at time of external beam radiotherapy (EBRT) were treated within the elective field. Additionally, EBRT boosts aiming at the macroscopic nodal disease were allowed. Frequency analyses of anamnestic, gynaecological and histological information, MRI findings and treatment related factors were performed for all individual patients as well as for the patient groups with or without nodal failure. Multivariable analyses were used to explore potential predictive factors for nodal failure in all patients, and for the groups ‘node positive’ and ‘node negative’ lymph nodes at diagnosis.

Results: During follow up (median 24 months, range, 3-60), 62 of the 857 patients developed nodal failure (7%), with 70% detected within the first year after treatment. Two year survival was 65% and 93%, respectively, for patients with and without nodal failure. Nodal failure occurred in 5% of the patients without positive nodes and in 10% of the patients with positive nodes detected on CT, MRI, US, PET-CT or by histopathology at time of diagnosis. In the subgroup of patients with positive nodes detected on PET-CT or histopathology proven lymph nodes, 15% had a nodal failure. Positive nodes at diagnosis were mostly located in the pelvic, whereas recurrences mainly occurred in the para-aortic (PAO) region (Figure 1). Isolated PAO failures were seen in 35% of the patients with nodal failure.

Cox proportional hazard analysis revealed positive lymph nodes at diagnosis, haemoglobin level < 6 mmol/L, white blood-cell count >10 x 10^9/L, and chemotherapy < 5 cycles as predictive factors for nodal failure. In the ‘node positive’ group FIGO stage was an additional predictive factor. In the ‘node negative’ group tumour width appeared to be the only prognostic factor for nodal failure.

Conclusions: The overall rate of nodal recurrences after (chemo-)radiation and MR-IGABT in advanced cervical cancer is low. The majority of nodal failures are located in the PAO region while affected lymph nodes at diagnosis are mostly seen in the pelvis. Two-year survival rates are significantly lower for patients with nodal failure. Lymph node involvement at diagnosis, haemoglobin level, white blood-cell count and chemotherapy are predictive for nodal failure.

OC-0487
The extent of synergy between tumor gamma-irradiation and checkpoint-blocking or T cell-recruiting antibodies
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Purpose/Objective: Combinations of local radiotherapy and immunotherapeutics have the potential to enhance local tumor control and to synergize in the induction of systemic antitumor immune responses. However, the optimal dose/fractionation regimens and optimal immunotherapy combinations still have to be defined. Here, we characterized the T cell responses induced by hypofractionated gamma-irradiation in a murine melanoma model and evaluated the extent of synergy of local tumor irradiation and PD-1 checkpoint-blocking or T cell-recruiting antibodies. PD-1 checkpoint-blocking antibodies enhance antitumor T cell responses; bispecific T cell-recruiting antibodies are capable of redirecting T cells to eradicate malignant cells. As monotherapy, both types of immunotherapeutics have recently shown dramatic efficacy in clinical trials in certain advanced malignancies, but it is not well understood to what extent they synergize with local tumor irradiation.

Materials and Methods: We used a subcutaneous flank tumor model by employing B16 melanoma cells expressing the prototypic tumor stem cell marker CD133, which is also a marker for melanoma stem cells. An antagonistic antibody blocking the PD-1 immune checkpoint on T cells or a bispecific (CD133×CD3) antibody recruiting T cells to CD133+ tumor cells was administered after hypofractionated irradiation of either small (200-250 mm^3) or large (500-750 mm^3) flank melanomas. Endpoints included tumor growth, overall survival, and immune infiltrate.
Radiation Oncology and technological innovation: a fish desperately looking for a bicycle?

D. Verellen

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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.

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

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

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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 aetiologic contribution differs in each anatomical location reflecting differences in natural history and viral tissue tropism. Up to 99.9% of cervixal, 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 CSCC 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 oncopogens E6 and E7 (HPV RNA), and (iii) alteration of steady state levels of cellular proteins, most consistently up-regulation of p16\\textsuperscript{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

Symposium with Proffered Papers: HPV and cancer and radiotherapy (HBN, cervix, vulva, anal)

SP-0489

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


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5General Hospital d'Hospitalitaet, Pathology department, Barcelona, Spain

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 challenge 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.

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 aetiologic contribution differs in each anatomical location reflecting differences in natural history and viral tissue tropism. Up to 99.9% of cervixal, 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 CSCC 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 oncopogens E6 and E7 (HPV RNA), and (iii) alteration of steady state levels of cellular proteins, most consistently up-regulation of p16\\textsuperscript{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