determine the treatment outcome. In this context, central questions in clinical particle radiobiology focus on the validation of RBE models, on the decipherment of underlying mechanisms, and on the question if a differential RBE between tumor and normal tissues exist.
The presentation will summarize the present knowledge of normal tissue effects after particle therapy with special emphasis on the RBE and its dependencies on physical and biological factors, on examples how RBEs for normal tissues are determined in preclinical models and from patient data as well as on needs of future investigations.

SP-0220
Novel radiation responses in normal tissue stem cells ñ Andante project
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There is growing evidence that the presence of stem cells is an important determinant for treatment outcome, not only for normal tissues but also tumours. Tissue/cancer stem cells are considered to be a main driver for tissue tolerance and regeneration and tumour growth, therapy resistance and relapse of disease. Recent developments in the field of adult stem cell technology have provided the possibilities of the 3D culture of multiple tissues and tumours as stem cell derived/containing spheres and organoids. These organoids closely resemble the composition of an organ or tumour and upon transplantation regrow the tissue and tumour closely resembling the original. Moreover, it has been suggested that adult stem are a critical target for radiation carcinogenesis. Stem cells are able to self-renew in tissues for a long period of time, which increases their lifetime risk of accumulating mutations required for cancer formation. Now using organoid cultures of salivary gland and thyroid gland we are able to study the radiation response of tissue and cancer stem cells in vitro. Examples of the response of spheres and organoids to X-rays, Carbon ions and Neutrons will be shown. Remaining organoid formation potential, self-renewal potential, stem cell marker expression, and differentiation potential, DNA repair and gene expression upon irradiation will be shown. Moreover, (xeno-)transplantation experiments allow assessment of actual regeneration potential of (cancer)stem cells. As such we now are potentially able to monitor and modulate the in vitro the response of tissues and tumours upon (chemo-) radiation and relate these to patient response and radiation-induced carcinogenesis.
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SP-0221
EGFR-inhibitors, radiotherapy and normal tissue toxicity
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EGFR-inhibitors have been used in several clinical settings during the last decade and side-effects related to normal tissues like the skin, mucosa and kidney has been well described. However, when EGFR-inhibitors are combined with radiotherapy, then different skin and mucosa toxicity profiles can be seen. The presentation will focus on typical as well as atypical clinical presentations of the combined treatment modalities in skin and mucosa. This will be with an emphasis on recent data from a randomized phase III trial on chemoradiation plus/minus EGFR-inhibition. The clinical presentations will be explained with references to the current knowledge of the biology of skin toxicity.
Treatment options for acute side-effects in skin and mucosa after bio-radiotherapy is rarely causal. A few attempts have been done; some of them aiming to rephosphorylate the EGF-receptor in the skin with vitamin K3. The talk will discuss the available data from these studies.
Across several tumour sites and for different EGFR-inhibitors, a correlation between skin toxicity and tumour response has also been documented. The reason for this correlation is not obvious but probably related to genetic alterations or certain genetic variations that are shared between tumour and normal tissue like skin and mucosa. At present, it is not possible to predict which patients that will develop severe skin toxicity and thereby potentially benefit from EGFR-inhibition in terms of tumour response. However, emerging data suggests that certain single nucleotide polymorphisms in the EGF-gene that alter the ligand-receptor binding might be responsible for the observed clinical correlation. These data will be discussed in the light of EGFR-inhibition in combination with chemotherapy and/or radiotherapy.

Symposium: Role of brachytherapy and contact X-ray in the treatment of rectal cancer

SP-0222
Role of endoluminal brachytherapy for rectal cancer: current status and challenges
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Clinical applications: High dose rate endorectal brachytherapy (HDREBT) is a highly targeted radiation modality that uses Magnetic Resonance Imaging (MRI) for target definition and computed tomography (CT) based treatment planning. The treatment is given on an outpatient basis and does not require anesthesia but conscious sedation as needed. In the era of Total Mesorectal Excision (TME) surgery, pre-operative external beam radiation therapy (EBRT) contributes by reducing the local recurrence from 11 to 5%. HDREBT was tested and validated clinically as an effective neoadjuvant modality for tumor down-staging in patients with operable rectal cancer having an advantage over the EBRT in providing limited normal tissues exposure to radiation. In patients unfitted for surgery, HDREBT was used as a boost after an initial course of external beam therapy to improve local control.
Technical applications: Pre-treatment includes imaging with pelvic MRI and tumor mapping with radio-opaque clips to improve the accuracy of treatment delivery. The patient is planned at the CT-simulator in supine position after bowel preparation with the Oncosmart intracavitary mold applicator (Elekta). Position of the applicator is adjusted to the level of the radio-opaque clips, as seen on the pilot, prior to CT scanning. Subsequently, the CTV contouring is performed based on MRI images. In the pre-operative setting, dose distribution is optimized in order for the target to receive 26 Gy in 4 fractions. In the boost setting, a repeated pelvic MRI is obtained 2-3 weeks after the external beam radiation treatment, period that allows tumor down-sizing, and the total dose 30 Gy is given weekly in 3 fractions. For this treatment the same applicator is used with tungsten shielding rod placed in the central applicator hole to protect the contralateral healthy tissue. Dose is optimized on the residual tumor gross tumor volume (GTV) with the addition of

a double balloon system introduced to optimize dose distribution.

Toxicity and long-term oncological results: In the neo-adjuvant setting, grade 3 radiation proctitis is observed in less than 0.5% of treated cases 7-10 days after treatment completion. In the boost setting, proctitis is observed 3-4 weeks after the HDREBT treatment and included rectal bleeding in 25% of the patients, out of which 10% with anticoagulation required transfusion and plasma-argon therapy. In 3 patients with circumferential tumors, rectal stenosis was documented. Rectal ulcerations can be observed 5-9 months after treatment but do improve over time. Overall for low T2 and T3 tumors, HDREBT resulted with a pCR rate of 27%, with the local recurrence of 4.8 % at 5 years with a median follow up time of 62 months. For the medically unfitted patients, with HDREBT used as a boost, the local control is 65% at a median 28 months follow up time.

Conclusion: In the present era of rectal preservation, the HDEBT represents a highly targeted radiation modality that is effective as neo-adjuvant and boost treatment modalities for patients with rectal cancer.

SP-0223

Role of contact x-ray brachytherapy (CXB) for rectal cancer: current status and challenges

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Surgery main Treatment of rectal cancer often combined with neoadjuvant (chemo) radiotherapy (CRT).

Despite improvement in local control for T2-3(4) tumors, CRT failed to improve conservative treatment in rectal cancer. Anterior resection is often associated with suboptimal bowel function. Organ preservation (whole rectum + anus) is gaining interest mainly for early (T1) T2 T3 tumors.

CXB: a unique technique of trans-rectal endoscopic Brachytherapy Evidence Based.

Mainly pioneered by Papillon in the 1970s the technique is presenting a renaissance since 2009 (1) with the manufacture of a new machine delivering high dose rate of 50 Kvp X-rays(Papillon 50™). Under direct endoscopic vision control it is possible to deliver 30 Gy in 2 minutes in a well-targeted small volume (5 cm^3). It is a fully ambulatory treatment feasible at any age with very low toxicity. The dose distribution is better than with Iridium endoluminal HDR brachytherapy and radioprotection is easier. The Lyon R 96-02 randomized trial (2-3) has demonstrated with a 10 year follow-up that CXB boost combined with External beam RT in T2 -3 low rectum was able to increase by 30% the rate of clinical complete response, of sphincter saving surgery and of organ preservation in case of cCR. The rate of perirectal nodal relapse is below 5%.

Present results in France and UK show good results for organ preservation in selected T1 T2 and early T3

In T1 N0 (or malignant polyps) treated with local Excision first (63 pts between 1986-2012 in Lyon and Nice), adjuvant CXB (50 Gy/ 3 fr/ 3w) achieved local control in 95% of cases with good bowel function. In T2 T3 less than ½ circumference and < 5cm diameter a combination of CXB and EBRT (or CRT), mainly in elderly frail patients, achieved cCR in close to 90% of cases (Lyon-Nice: 120 pts) with less than 20% local relapse very exceptional in perirectal lymph nodes (4-5). In Clatterbridge-Liverppool same results were achieved in the recent past years in more than 150 pts. Such combined CXB+ CRT appears as a very good option for frail patients or for younger patients adamantly refusing an invasive surgery.

Many challenges remain open

In operable patients the upcoming OPERA randomized trial will like the Lyon R96-02 try to show that CXB in addition to CRT (CAP 45) may achieve in T2 T3a-b at least 40% of organ preservation with good bowel function. The new machine Papillon+™ will bring some technical improvements. But the most important issue is that radiation oncologists willing to use CXB must get a good clinical practice of rigid rectoscopy on an ambulatory basis.

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SP-0224

Endoluminal radiotherapy in rectal cancer: Which questions do we need to answer?

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In the treatment of rectal cancer, total mesorectal excision surgery is now the standard of care. In most patients, surgery will be preceded by external beam radiotherapy (EBRT), either in a short course (25 Gy/5 fractions) or in a conventional schedule (45-50 Gy/25 fractions) with chemotherapy. Brachytherapy (BT) is an appealing alternative to EBRT. In comparison to the EBRT, it offers the advantage of delivering a high dose of radiation with a rapid dose fall-off around the site of interest (tumor target). This results in the sparing of normal tissues such as small bowel but also the bladder, the prostate, anal sphincter and skin.

In order to understand why brachytherapy may work as replacement for external beam radiotherapy, an exact target volume definition for rectal cancer is required, based on precise data on the local recurrence patterns. The decision which nodal regions should be included in the clinical target volume is often topic of discussion. In general, it can be stated that the highest risk of lymph node involvement is in the mesorectal fat. In addition, the presacral space and the internal iliac region are at risk. Depending on the exact localization and tumor stage, the obturator nodes, the external iliac nodes and the inguinal nodes may sometimes be affected. For years, this has lead to a more or less standard clinical target volume, including the primary tumor, the mesorectal fat and the presacral and internal iliac lymph node regions. However, given the limited number of recurrences after TME surgery, the standard clinical target volume can be seriously questioned.

Another interesting application of endoluminal brachytherapy is the ability to increase the dose on the primary tumour. In elderly patients, standard surgery may be hampered by the