traditionally done by physicians or physicists and play an important role in the multidisciplinary implementation of new treatment techniques. There are now significant opportunities for RTTs to develop their role within the radiotherapy team, promote excellence in patient care and engage in research.

SYMPOSIUM: NORMAL TISSUE TOLERANCE: INDIVIDUALISED TREATMENT

SP-0116
Extension of dose-volume metrics using imaging
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Relationships between dose delivered to an organ at risk and radiation-induced complications have been studied for many years. Complications are often either dichotomised (present or not present) or coarsely graded using a 4-point scale. The three-dimensional dose distribution over a particular organ is also typically summarized using a simple mean dose, or as a dose-volume or dose-surface histogram (DVH or DSH). Thresholds, such as the volume receiving more than given dose (V_d) can be extracted from the histogram, or the histograms can be reduced further to a single number expressing normal tissue complication probability (NTCP).
DVH reduction models have shown some success in predicting clinical outcomes, but all spatial dosimetric information is lost. For hollow organs, such as the rectum, models explicitly including the shape of dose distribution have been shown to provide stronger correlations with outcome than simple DSHs. Furthermore, different toxic end points have been shown to be associated with different features of the dose distribution: rectal bleeding with lateral extent of the dose distribution and loose stools with longitudinal extent, whilst proctitis was associated most strongly with the DSHs itself. This indicates that, in addition to improving predictive power, the inclusion of spatial information in the NTCP model also has the potential to give insight into the mechanism behind various toxicities. The 2-dimensional DSH-based models can also be extended consider the 3-dimensional dose distribution: dose tolateral and cranial component of parotid gland during head and neck radiotherapy has been shown to increase the risk of xerostomia. Interestingly, non-dosimetric factors were also included in this modelling and submandibular gland removal was shown to be an independent risk factor for xerostomia.
The clinical severity of radiation-induced toxicity to a large "parallel" organ may depend on the baseline functional reserve. Lung perfusion SPECT or hyperpolarized gas ventilation MRI have been shown to be capable of mapping baseline lung function in lung cancer patients. Predictors of toxicity such as perfusion-weighted mean lung dose or perfusion-weighted DVHs can then be used to more accurately estimate the effects of treatment. These "functional DVHs" have been demonstrated to be useful for creating radiotherapy plans which preferentially avoid healthy, well-perfused lung. Similar approaches are also possible in the treatment of liver cancer, where it has been shown that maps of baseline function can be produced using dynamic contrast-enhanced CT, HIDA, GSA or mebrofenin SPECT and FDGal PET.
In summary, the predictive power of traditional DVH reduction methods which summarize the 3D dose distribution in an organ at risk with a single number has been shown to be improved by adding additional information. Spatial dosimetric information has been shown to not only give stronger associations with treatment outcome, but also give insight into the mechanism behind various toxicities. Functional imaging can help assess functional reserve in parallel organs, allowing selective avoidance of healthy portions of damaged organs such as the liver and lungs and hybrid models incorporating dosimetric and non-dosimetric information have shown promise. To be useful in routine clinical practise implementation within commercial treatment planning systems and dose optimisation engines is required, together with more extensive validation against clinical outcome data.

SP-0117
Comorbidity
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Abstract not received

SP-0118
Genetic tools for prediction of normal tissue response; Perspectives and obstacles
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The ability to predict individual risk of radiation-induced normal tissue complications is a long sought goal in radiobiology. During the last decade, substantial efforts have been made to establish a gene based predictive test for normal tissue radiosensitivity. Around 80 candidate gene studies have explored possible associations between SNPs and the risk of normal tissue complications after radiotherapy. Although around two-thirds of the studies reported significant associations, the results have been very inconsistent and independent confirmation of the associations rarely took place. In hindsight, it seems obvious that many of the studies published so far have suffered from severe methodological shortcomings of which insufficient statistical power and lack of correction for multiple testing are among the most prominent (1).
After quite a teething period, substantial progress is currently being made in radiogenomic research. A number of important lessons have been learned from other research fields (2). There is a growing consensus that studies addressing SNPs need to be powered to detect rather small differences in toxicity risk. Two of the largest SNP studies ever conducted in normal tissue radiobiology, including more than 1,600 and 2,000 patients, have recently been published (3,4) of which one actually reports a compelling association for a SNP near the TNF-alpha gene. Cooperative research groups are increasingly active in the field. A large international meta-analysis addressing a TGF-beta1 SNP, comprising individual patient level data on 2,782 patients from 11 cohorts, has been published (5). The first genome-wide association study in normal tissue radiobiology has been conducted and more are underway. These developments are certainly warranted and heraldt hat interesting discoveries will be made in the years to come. Nevertheless, the human genome has some fundamental characteristics that are challenging to deal with from a statistical point of view. Furthermore a number of clinical and dosimetrical issues need to be taken carefully into consideration in radiogenomic research (6).

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SYMPOSIUM: BRACHYTHERAPY AS A BOOST

SP-0119
The radiobiology and physics of brachytherapy boost
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Radiobiology and physics are closely coupled in considering the benefits versus the concerns of delivering brachytherapy, particularly as a boost in an already irradiated volume. Clearly, it is essential that the target volume is easily accessible to placement of intracavity applicators, catheters or seeds particularly if the brachytherapy is fractionated. Therefore brachytherapy tends to be most adopted as an alternative or additional modality to external beam delivery in the treatment of cancers in cervix, anus, rectum, head and neck, prostate, breast and skin.
Since the source of radiation dose in brachytherapy is within the target volume, the dose fall-off outside the target volume is much more rapid compared with external beam treatment plans. For example comparing irradiation of prostate using high dose-rate brachytherapy with external beam plans, dose fall-off is 4-5 times greater with distance away from the organ in the brachytherapy. This more rapid dose fall-off outside the target volume also gives a major

benefit to brachytherapy in a boost situation, and in retreating recurrent cancer where it may be necessary to restrict reirradiation of critical structures that received significant dose in the first treatment.

Though permanent I125 seed implants have been successful in delivering low-dose-rate brachytherapy to prostate, most brachytherapy now uses high dose-rate plans from Ir192 which have the advantage that more precise dosing is obtained by modern remote afterloading systems which can vary dwell times at each position of the source. Radiobiologically, high dose-rate delivery is also advantageous in sparing late-reacting normal tissue where repair is usually slower than in the malignancy, though this biological advantage does require high dose-rate brachytherapy to be fractionated.

SP-0120
Brachytherapy for the closest boost in breast cancer.
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Introduction: In breast cancer, the target volume for a boost to the high risk area of residual disease is the primary tumour bed including the surrounding breast tissue. Especially in Europe, the use of brachytherapy (BT) as a boost modality is gradually being replaced by 3D-CRT photon beam techniques because of logistic reasons. However, multi-catheter interstitial BT remains popular, especially for APBI, and is being investigated for treatment of recurrences/new primaries in the same breast.

Technical aspects: Especially tumours located centrally or peripheral in the breast are suited for treatment with BT. Rigid or flexible afterloading catheters are placed under anaesthesia in the breast tissue around the lumpectomy cavity. The number of catheters depend on the size and shape of the target, in agreement with BT guidelines. Most often 5-9 catheters are positioned at 1-2 cm distance in 1-3 planes to ensure adequate coverage and a homogeneous dose. The lumpectomy cavity can be identified by pre-operative imaging, palpation, per-operative ultrasound or radio-opaque clips positioned during surgery. A template is used to properly position the catheters. A planning-CT scan for dosimetry is made the day after the implantation to allow resolution of swelling. The CTV is delineated as the lumpectomy cavity with a margin in all directions (often 1-1.5 cm) in the breast tissue, thereby excluding the skin (at least 5 mm) and pectoral muscles. Currently, a PDR (15-20 pulses of 1 Gy) or HDR (7 Gy) [192]Ir after-loader is mostly used. 3D-TPS dwell-time optimisation is used based on the CTV taking into account the implant geometry.

Results: In the EORTC "boost-trial"[1], a total of 2661 patients received a boost dose of 16 Gy after complete tumour resection. The boost technique was: 63% direct electron field, 28% photon beams and 9% interstitial BT. The 10-year cumulative incidence of local relapse was 6.3% for electrons (95% CI. 5.1-7.5%), 5.3% for photons (95% C.I. 3.6-7.0%) and 3.7% for BT (95% C.I. 1.2-6.2%) (p = 0.13). The occurrence of (any grade of) fibrosis was similar in the 3 groups: 70%, 66% and 72%, respectively. Harms[2] treated 113 patients with risk factors for local control (close or positive margins, vascular invasion, T2G3) with an interstitial PDR boost of 15-25 pulses of 1 Gy. At 5 years, the actuarial local recurrence-free survival rate was 95%. Grade 3 skin or soft tissue toxicity developed in 10.8% of patients treated with a boost of ≤20 Gy and 54.6% of patients treated with >20 Gy (p < 0.01). Cosmetic outcome was scored as excellent or good in 90% by patient assessment, and in 80% by physician assessment. Niehoff[3] found no difference in the outcome between interstitial HDR or PDR BT in re-irradiation for breast or chest wall recurrences of 32 patients.

Advantages and challenges: As with BT the implant moves together with the lumpectomy cavity, no supplementary margin is required to obtain the PTV. Moreover, the shape and size of the surgical cavity is less important as irregularly shaped cavities can be conformally treated using modern treatment planning techniques. Oncoplastic resection and reconstruction techniques offer a challenge for proper localisation of the CTV, with BT offering the advantage of the ability to shape the treated volume based on imaging and marker clips positioned around the primary tumour bed. As anaesthesia is required for the implant procedure, a challenge remains to either perform it under local anaesthesia or to per-operatively combine it with tumour resection. Delivering BT according to current standards requires specialised training and experience of a team consisting of radiation oncologists, medical physicists and radiation technologists.

Conclusions: The brachytherapy technique has several advantages and therefore will continue to be used, especially for APBI. In addition, an appealing new feature lies in its use as secondary breast conserving treatment.

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SP-0121
Brachytherapy as a Boost. Prostate
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High-dose-rate (HDR) brachytherapy is an established curative treatment option for patients diagnosed with prostate cancer. Several advantages of HDR brachytherapy over other radiotherapy techniques have been identified: (1) the accurate positioning of the sources by first implanting non-active guide needles, (2) the possibility to exactly choose the position of the source over the entire length of every single needle, (3) the absence of any target movement during irradiation, (4) the possibility of "on line" adjustments of dwell source locations according to 3D planning based on individual dose prescription, (5) the absence of any need for pre-implant needles preparation, and finally (6) a safer radio-protection profile as compared to permanent seeds implant procedure.

The greatest clinical experience with HDR for prostate cancer involves its *combination with EBRT*. A systematic review of available literature has compared EBRT alone (at doses > 75 Gy), EBRT combined with HDR brachytherapy boost and EBRT combined with LDR permanent seeds boost in terms of efficacy endpoints. Despite the fact that patients treated with EBRT+HDR boost had more advanced disease, both biochemical disease free survival (biochemical Not Evidence of Disease, bNED) and overall survival rates were significantly better with this combination. Moreover the results of the only phase III randomized trial available in this field comparing EBRT alone (55 Gy in 20 fractions) versus a combined EBRT (35,75 Gy in 13 fractions) + a HDR boost of 2 fractions of 8,5 Gy showed a significant advantage in bNED favoring the combined arm.

Acute toxicity consists of mild LUTS (dysuria, urinary frequency, urgency) in 40 to 60% of patients but grade 3 genito-urinary (GU) symptoms are only presents in 1-5%. The return to base-line values is obtained much earlier than after LDR brachytherapy. In the immediate post-implant hours, hematuria is also relatively common but resolves rapidly . Urethral stricture is the most frequent non-trivial *late toxicity* reported occurring in the bulbo-membranous urethra in more than 90% of the cases. Overall, it develops in 5 to 15% of patients with patient-related predictors being identified such as a prior history of TURP, an elevated pre-implant IPS-Score, older age, prostate volume (and use of neo-adjuvant ADT for pre-implant downsizing) and hypertension but also with a number of treatment-related ones (HDR dose per fraction, number of midlines needles implanted, a long Z-axis of the CTV). Incontinence is less common and typically related to post-implant need of a TURP. *Gastro-intestinal* (GI) toxicity is frequently dependent on EBRT protocol adopted (irradiated volumes, prostate alone versus pelvis ± prostate CTV, dose/fraction to the pelvis) with grade 3 toxicity reported occasionally and proctitis, anal pain and rectal bleeding occurring in less than 5% of patients in all published papers.

Several areas remain for further investigations and should be explored in future trials. **(1)** The optimal dosing regimens is still unclear: the first published series adopted HDR schedules of two or more fractions while recently protocols proposing a single fraction/implant have been developed with encouraging early results thus minimizing the risk of potential needles/catheters displacement between fractions. **(2)** HDR brachytherapy has been proposed for local salvage after biopsy proven intraprostatic relapse of irradiated prostate cancers with encouraging results but larger series with longer follow-up are needed to fully validate this strategy . **(3)** The typical inhomogeneous dose distribution obtained with brachytherapy techniques can be exploited in view of a "focal irradiation" of the prostate for carefully selected patients harboring limited unilateral cancers. **(4)** Costs of temporary HDR brachytherapy are limited. Rigorous cost-analysis and comparisons between therapeutic alternatives have so far never been attempted but if HDR brachytherapy techniques are able to convincingly demonstrate a cost-effective advantage as compared to other therapeutic options for localized prostate cancer, the procedure is likely to be offered in the near future to increasing numbers of patients.

SP-0122
Brachytherapy boost with complementary external beam irradiation in anal canal cancer
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Introduction: Primary radiotherapy in form of external beam radiotherapy (EBRT) combined withchemotherapy or combined with local dose escalation by brachytherapy enables anal sphincter