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ABSTRACTS

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Type: Biology

CD8+ cytotoxic T cells mediate the high treatment efficacy of Microbeam Radiotherapy in radio-resistant melanoma

Type: Biology

Presenting Author:
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Aims: Synchrotron-generated Microbeam Radiotherapy (MRT) is an innovative radiotherapy modality that spatially fractionates X-rays into microbeams delivered at FLASH dose-rates. Recently our group tested MRT on radioresistant B16-F10 melanomas implanted in mice ears. We proved that MRT significantly delays tumor growth compared to a homogenous broad beam (BB) irradiation resembling conventional radiotherapy. We underlined some biological mechanisms behind MRT efficacy, such as vasculature disruption, arrest of proliferation and induction of cell senescence. In the present study, we aimed to investigate whether the immune response plays a major role in MRT tumor control effect, in particular cytotoxic T cells (CTLs).
Methods: Melanomas received either MRT (400 Gy peak-dose, 50 µm beam width, 400 µm spacing), BB (6.2 Gy) or no treatment. Six to 8 tumors per group were harvested at 2, 5 and 7 days post-irradiation (dpi) and their immune composition was investigated by flow cytometry. Subsequently, after confirming that the CD8+ T cells were successfully depleted in melanomas using an InvivoMab CD8 (Bio X Cell) compound, we tested the combination of CD8+ CTL depletion and MRT, BB or unirradiated controls relative to their non-depleted counterparts.
Results: No major difference within the myeloid cell content (e. g., macrophages, granulocytes) among the different treatments was found. However, at 7 dpi, we detected a higher T cells infiltration, specifically CD8+ CTLs, in the MRT group compared to the BB group and unirradiated controls. We hypothesized that the infiltration of CTLs is fundamental for MRT-induced tumor growth delay. As a proof of concept, we investigated if the MRT effect can be reversed by depleting CD8+ T cells. MRT-treated mice undergoing CD8+ CTL depletion showed a significant decrease in survival rates, median survival times and tumor growth rates, compared to the mice that did not receive the Mab treatment. The Mab treatment had no significant effect on unirradiated controls and BB groups.
Conclusion: CTLs are essential to elicit MRT efficacy in murine melanoma. This study contributes to understand how MRT controls radioresistant tumors.

The parameters of the Lyman model: a systematic literature review

Type: Biology

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Aims: We attempted to collect the entirety of radiobiological parameter sets published for the Lyman model, being one of the most frequently used models for calculation of normal tissue complication probability (NTCP) in radiation oncology. Aim of the work was to provide an overview of the data basis of the model for different radiooncological situations. Furthermore, we wanted to compare the parameter values and calculated NTCPs for selected endpoints with sufficient data available.
Methods: A systematic literature analysis was performed searching for publications that provided parameters for the different variations of the Lyman model in the Medline database using PubMed. Parameter sets were grouped into 13 endpoint groups that were identified during the research. For the three selected endpoint groups "reduction of saliva ≤25% twelve months after irradiation of the parotid", "symptomatic pneumonitis after irradiation of the lung" and "bleeding ≥ grade 2 after irradiation of the rectum" we compared parameter values and analyzed differences in calculated NTCP values.
Results: A total of 509 parameter sets from 130 publications were identified. We detected considerable heterogeneities regarding the number of parameters available for different radio oncological situations. Furthermore, for the three selected endpoints we found large differences in published parameter values. These translate into large differences of calculated NTCPs, with maximum ranges of 35.2–93.4% for the saliva endpoint, of 39.4–90.4% for the pneumonitis endpoint and of 5.4–99.3% for the rectal bleeding endpoint.
Conclusion: Appropriate selection of parameter values is necessary when using the Lyman model for calculation of NTCP. Calculations must be interpreted with caution–not only due to general limitations of the model, but also due to variances of parameter values published in the literature.

Could hyper-radiosensitivity to low-dose phenomenon explain Cyberknife efficiency?

Type: Biology

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Aim: to characterize the specific radiobiological effects of SBRT in human HRS-positive and HRS-negative tumour cell lines, in the frame of the RIANS model. stereotactic body radiation therapy (SBRT) permits to deliver high doses in few sessions. Hypofractionation of the dose has been evoked to explain the SBRT efficiency, although considering additive effect of some Gy separated from few days fails to provide a relevant and actual specificity. By contrast, each SBRT session is divided into several hundred microbeams of low dose converging to the tumour with a sub-millimetric precision. Hence, this hyperfractionation of the dose (lower than one Gy) delivered by each microbeam invokes the phenomenon of hyper-sensitivity to low dose (HRS) repeated several times [1]. Furthermore, the HRS phenomenon has been described through the radiation-induced ATM protein nucleoshuttling (RIANS) model [2].
Methods: human tumor cell lines were cultured to confluence, and then irradiated by CyberKnife® (Accuray, USA) according to several different fractionation schemes. After irradiation, ATM, H2AX, and MRE11 proteins were tracked by immunofluorescence technique.
Results: one SBRT session of 2 Gy produced much more unrepaired DNA double-strand breaks than a single dose of 2 Gy, a single dose of 0.2 Gy, or else a repetition of 10 doses of 0.2 Gy in 5 HRS-positive

versus 2 HRS-negative human tumour cell lines. Besides, some highly damaged cells specifically appeared in Cyberknife® conditions while they were absent with the single-dose conditions.
Conclusion: the RIANS model may provide a relevant biologically explanation of the SBRT efficiency. In each submillimetric region of an HRS-positive tumor, the effect of low doses hyperfractionation may be much higher than the cumulated physical dose per session.

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p53-dependent treatment response to DNA-PK inhibition in combination with irradiation in head and neck squamous cell carcinoma models

Type: Biology

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Aims: M3814 is a small-molecule inhibitor of DNA-PK, a key regulator of nonhomologous end joining (NHEJ). Inhibition of NHEJ along with irradiation (IR)-induced DNA double-strand breaks can potentially increase antitumor treatment efficacy. This study aims to investigate responses of head and neck squamous cell carcinomas with distinct HPV and p53 status to the treatment with IR, DNA-PK inhibition, and their combination.
Methods: Three groups of cell lines with various HPV/p53 genotypes (p53-wt/HPV–; p53-mutated/HPV–, and p53-wt/HPV+) were treated by M3814, 4 Gy IR, or a combination of M3814 and IR. In addition to viability and cell cycle assays, caspase 3 activity and senescence-associated β-galactosidase assays were used to evaluate cell fates such as apoptosis and senescence. yH2AX and RAD51 foci immunostainings at different time points were implemented to assess the levels of DNA damage and its repair. NMRI-nu mice with subcutaneous xenografts of p53-wt/HPV+ and p53-wt/HPV- cell lines were treated with either fractionated 10 Gy IR (delivered with the small animal radiation therapy system SmART) alone or in combination with orally distributed M3814.
Results: Decreased number of viable cells after IR alone and particularly after combined treatment was observed in most of the cell lines. Inhibition of NHEJ combined with IR induces an abrogation of proliferation with different cell fates. Whereas HPV+ and p53-mutated cells undergo apoptosis due to a common alteration in the p53 pathways, p53-wt cells are preferentially eliminated through senescence. Elevated yH2AX foci formation after 24 and 48 h in the combination treatment group indicates unresolved persistent DNA damage. In vivo, significant effects of IR and of the combination treatment on tumor growth control were observed particularly in p53-wt/HPV+ xenografts.
Conclusion: M3814 radiosensitizes HNSCC tumors and leads to better treatment response in dysfunctional p53 cells. Determination of the HPV and p53 status in a particular tumor might be necessary to effectively shape the intervention outcome when combining NHEJ targeting with radiation therapy.

Exploring the dual role of SPRR2A in invasiveness and therapeutic resistance in head and neck squamous cell carcinoma

Type: Biology

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Aims: Head and neck squamous cell carcinoma (HNSCC) remains one of the most common cancers world-wide. However, resistance to RT, a mainstay of treatment for this disease, is one of the main reasons contributing to treatment failure and a thorough understanding of underlying molecular mechanisms is needed to address it therapeutically. To this end, we recently analyzed genomic and transcriptomic profiles of patient-matched head and neck cancer cell lines from primary and secondary (either recurrent or metastatic) disease. Gene coding for small proline reach protein 2A (SPRR2A), a protein previously known primarily for its role in maintaining epithelial tissue homeostasis, was found to be the most differentially regulated gene in both metastatic and recurrent cell lines compared to their matched primary counterparts. Our current study aims to elucidate its role in pathogenesis and radiation resistance of HNSCC.
Methods: Two cellular models with either knocked-out SPRR2A expression (using CRISPR-Cas9 gene editing) or its stable overexpression (using lentiviral transduction of wild type or mutated gene) have been generated and used in a series of in vitro and orthotopic murine in vivo experiments.
Results: SPRR2A expression is upregulated in HNSCC cell lines following exposure to ionizing irradiation (IR). Ectopic expression of SPRR2A protects cells from IR-induced DNA damage. Moreover, SPRR2A forms a complex with both MDM2 and p53, thereby affecting their stability. This consequently influences cell cycle progression and cell survival, in particular upon exposure to IR. The formation of the SPRR2A-p53 complex seems to be stimulated by SPRR2A-Y67 phosphorylation, the effects of which are currently being studied.
Conclusion: Our study has the potential to shed new light on understanding of molecular pathogenesis in radiation resistance and recurrence risk and be of diagnostic and therapeutic value to HNSCC patients.

Metastacic Surveillance Post Microbeam Radiotherapy

Type: Biology

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Aims: Experimental synchrotron-generated Microbeam Radiotherapy (MRT) targets tumours with a heterogenous radiation field, fractionated into micrometer-wide planar, high-dose beams, separated by regions of low dose deposition. MRT elicits an enhanced therapeutic ratio compared to conventional radiotherapy, however, metastasis has never been used to assess the effectiveness of MRT. We investigated an

association of MRT regimens, local control and metastasis in two metastatic mouse tumour models.
Methods: B16-F10 melanomas in C57BL/6J mice and 4T1.2 mammary carcinomas in BALB/c mice were irradiated with various MRT and/or broad-beam (BB) regiments. We measured the primary tumor volume, survival, and metastases (by scoring a B16-F10 infiltrate in cervical lymph nodes, or by RT-QPCR analysis of 4T1.2 metastatic burden in lungs). In the melanoma model, quantitative Bioplex and ChipCytometry analyses were used to measure plasma cytokine levels and immune cell lineages infiltrating the primary tumour.
Results: 1) Three daily MRT fractions resulted in complete ablation of 50% B16-F10 melanomas, with no metastasis in the cured animals. 2) A second MRT fraction for B16-F10 melanoma, given 10 days after the first MRT, promoted both local and locoregional control. The increase of CXCL5, CXCL12, and CCL22 cytokine levels after the second MRT suggested that the inhibition of melanoma progression may be associated with increased activity of antitumor neutrophils and T-cells. Indeed, the infiltration of neutrophils and activated T-cells in the tumours increased after the second MRT. 3) A fractionated irradiation regime combining one MRT and two BB irradiations for the 4T1.2 carcinoma was more efficient than fractionated MRT or BB alone, in terms of local control and metastasis. No acute toxicities have been observed in the treated mice.
Conclusion: Our study highlights the importance of post MRT metastatic surveillance and provides the first MRT fractionation plan that promote local and locoregional control and have the potential to control distant metastasis. The unique MRT geometry triggers a spectrum of immune responses that contribute to the antitumor effect of MRT.

MET-targeting CAR T cells enhance tumor cell killing and cytokines release in glioma models when combined with radiation therapy

Type: Biology

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Aims: Glioblastoma (GBM) is the most frequent primary brain tumor with dismal prognosis after radiation therapy, a standard treatment option for this disease. Recently, RT has been investigated as a mediator of effects of T cell-based therapies in the context of immunosuppressive GBM microenvironment. The MET receptor is an oncogene involved in radiation response, radiation resistance, and stem-like properties of GBM. We study the impact of MET-targeting chimeric antigen receptor (CAR) T cells (MET-CAR T cells) combined with radiation in GBM, and hypothesize that this combination acts synergistically in terms of tumor growth control.

We co-cultured MET-CAR T cells with adherent (2D) and stem-like (3D) human GBM cells with or without RT and assessed the killing efficiency and cytokine production of CAR T cells.
Results: Our results indicate that 5 Gy radiation combined with MET-CAR T cells increases their potential in tumor cell killing. We observed increased CAR T cells effect at lower CAR T to target cells ratios when combined with radiation, even when radiation treatment alone did not lead to a significant decrease in GBM cell viability. This phenomenon was similar in both types of cell lines as well as across different levels of MET expression, and different sensitivity to CAR T cells. The mechanisms behind this observation were investigated via intracellular cytokine measurements.

The most prominent response was in TNF-a expression. Increase in Granzyme B expression was observed in co-culture with some of the GBM cell lines and was more prominent in CD8+ subpopulation of CAR T cells. An increase in IFN-gamma was observed in some adherent glioma cell lines but was absent in co-culture with stem-like glioma cell lines. Our pilot in vivo study in orthotopic GBM model demonstrated tumor reduction after 48 h of intravenous and intracranial injection of MET-CAR T cells. The RT-CAR T combination studies are to follow.
Conclusion: our data demonstrates the potency of MET-CAR T cells against GBM, and increased efficiency when combined with radiation. The suggested mechanism is the increased activation of T cells in TNF-a-dependent-manner.

Mechanisms of normal tissue recovery following high-dose, microbeam radiation therapy

Type: Biology

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Aims: Microbeam Radiation Therapy (MRT) is the spatial fractionation of synchrotron-generated X-rays into an array of parallel, evenly spaced, microbeams, 50–100 μm in width. This unique geometry of heterogenous dose deposition allows for the delivery of hecto-Gray doses in a single fraction. In the past few years, the radio-oncology community has intensively discussed the clinical implementation of MRT identifying the need for further clarification of the radiobiological mechanisms of action for future application. Spatial fractionation minimizes the volume of normal tissue receiving high doses of radiation and it is hypothesized that normal tissue in the unirradiated/low dose regions act as centres of regeneration promoting tissue recovery and prevention of long-term damage. Although a key hypothesis behind MRT's normal tissue tolerance, this phenomenon has never been demonstrated in vivo.
Methods: Using the unique tissue model of the mouse ear pinnae, cutaneous regeneration responses were assessed, following MRT irradiation of 200, 400 and 800 Gy peak doses with a microbeam array composed of 50 microns wide beamlets spaced 200 microns apart. The Ki67 proliferation index was spatially quantified over time by immunofluorescence detection.
Results: MRT induces a dose-dependent increase in normal tissue proliferation with spatial distribution corresponding to areas of peak dose deposition by day 15 post irradiation. This is the first depiction of the hypothesized phenomenon behind MRT's normal tissue tolerance to exceptionally high dose deposition. After, MRT, minimally irradiated normal tissues in the valley regions bridge/repopulate the 50–100 μm peak.
Conclusion: This regeneration is unique to normal tissue and a key process in wound repair, providing mechanistic evidence behind the effective normal tissue sparing following MRT. This has the potential to act as a predictive marker of long-term tissue preservation to extremely high radiotherapeutic doses delivered with this strategy and assist in determining dose tolerance thresholds in various tissue types.

Genomic characterization of head and neck squamous cell carcinomas and their patient-matched lymph-node metastases

Type: Biology

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Aims: Head and neck squamous cell carcinomas (HNSCC) account for more than 500,000 annual cancer-related deaths worldwide. Lymph node (LN) metastases represent a critical prognostic element in HNSCC as the survival of patients with LN metastases is nearly half compared to patients without LN spread. Here, we aim to genomically characterize matching primary tumors and LN metastases of a large retrospective cohort of HNSCC patients with long follow-up.
Methods: We performed whole-exome sequencing of normal tissue, primary tumors, and LN metastases from 104 HNSCC patients. All samples were obtained prior to treatment. Alignment and mutation calling was performed using the bcbio v.1.1.7 pipeline. SigProfiler was used to fit mutational signatures. Clonality and phylogenetic analyses were done using absolute and phylogicNDT.
Results: Patients had an average age at diagnosis of 59 years, were mostly male (79%), and most had exposure to known HNSCC risk factors. WES analysis found a median of 122 and 109 mutations in the primary tumors and the metastases, respectively. The gene mutation frequency did not differ between primary tumors and metastases. 58% of patients had at least one actionable alteration in either the primary tumor or the metastasis. We identified seven mutational signatures from the COSMIC catalog that contribute more than 92% of all mutations. Albeit highly heterogeneous among the patients, signature activity showed little differences between primary tumors and metastases.

Clonality analysis identified an average of five mutation clusters per patient. All but one primary sample (98.9%) and all metastatic samples had at least one subclonal cluster. Mutation signature activity was dynamic through the evolution of the tumors. In primary tumors and metastases, respectively, the contributions of SBS10b and SBS2 + 13 were higher for late mutational events.

A low fraction of shared mutations and the activity of signature SBS16 were significantly associated with a lower risk of locoregional recurrence.
Conclusion: This is the first study providing a genomic characterization of a large cohort of matched primary HNSCC tumors and their lymph node metastases.

DNA damage response and synthetic lethal targets in CHK2-deficient cancers

Type: Biology

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Aims: Checkpoint kinase 2 (CHK2) participates in the DNA damage response (DDR) by regulating cell cycle checkpoints or inducing apoptosis. Thus, CHK2 abnormal activity can lead to cancer development. CHK2 loss-of-function mutations have been correlated with the onset of many types of tumors and with therapy resistance.

Hence, our aim is to understand how CHK2 deficiency is affecting DDR and repair and to exploit the concept of synthetic lethality to target selectively CHK2-deficient cancers.
Methods: CHK2-proficient (WT) and -deficient (KO) human isogenic HCT116 colorectal cancer cell lines were used. DDR was assessed by γH2AX and RAD51 foci formation and by a Traffic Light reporter assay following DNA double-strand break (DSB) induction in combination with DNA-PK and RAD51 inhibition.

CRISPR/Cas9 screening with a library of 5070 kinases-targeting sgRNAs and cell-based assays were employed to identify CHK2 synthetic lethal partners and to validate them in a panel of CHK2-deficient cancer cell lines, respectively.
Results: Our results show a significant increase in basal and post-irradiation γH2AX foci levels, and compromised RAD51 foci formation in CHK2 KO cells compared to the CHK2-proficient ones. Simultaneously, CHK2-deficient cells exhibit higher homologous recombination repair (HRR) frequency than their CHK2 WT counterparts. In line with these observations, transcriptomics analysis revealed a significantly decreased expression of DNA-PKcs in CHK2-deficient cell line compared to CHK2-proficient one, an observation confirmed also on a protein level. Besides, the CRISPR/Cas9 screening and further validations identified two kinases as synthetic lethal partners of CHK2.
Conclusion: CHK2 deficiency strongly affects DDR and the choice of DSBs repair pathway upon DNA damage.

Pending further experiments, pharmacological targeting of the kinases identified as CHK2 synthetic lethal partners could become a plausible treatment strategy for CHK2-deficient cancers.

Type: Clinical

Effect of hyperthermia when combined with radio(chemo) therapy for treatment of pelvic tumors

Type: Clinical

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Aims: A retrospective analysis was performed to evaluate the effect of deep regional hyperthermia (HT) when combined with radio(chemo) therapy (RCT) in patients with pelvic tumors.
Methods: In total 31 patients (n) with pelvic tumors were treated with curative (subgroup I, $n = 20$) or palliative intent (subgroup II, $n = 11$) between 2017–2021.

The overall survival (OS) and progression free survival (PFS) rates were analyzed. The complete response (CR) rate was also assessed for subgroup I. Tumor-temperature achieved at x% (Tx) of all measurement points and cumulative equivalent minutes at T90 (CEM43°CT90) for each HT session were calculated using Rhythym [1].

Table 1 Analysis of temperature parameters for patients with recurrent and nonrecurrent tumors

Tumor temperature parameter (°C) [HT session]	Nonrecurrent tumors	Recurrent tumors	*p*-value
T50[1]	40.6	39.5	0.01
T50[3]	40.6	39.5	0.01
Tmin[1]	39.2	35.6	0.01
Tmin[3]	39.4	35.3	0.003
T90[1]	40.1	37.5	0.02
T90[3]	40.7	37.1	0.003

Results: Patients in subgroup I and subgroup II received total radiation doses of 30–61.2 Gy and 26–54 Gy (one patient received a brachytherapy boost) with median of 5 HT sessions, respectively. Chemotherapy was administered in 45% of patients. In total, 20% of treated tumors were recurrent in subgroup I and and 64% in subgroup II. The 1-year and 2-year OS rates were 85% and 75% for group I and 72% and 54% for group II, respectively. The 1-year PFS rates were 63% for subgroup I and 66% for subgroup II. Patients from subgroup I had a 1-year CR rate of 83% (95% CI: 55–95%). Significant differences of T50, Tmin and T90 computed with mean of 14 and 7 measurement points in 11 patients with nonrecurrent and recurrent tumors, respectively, were detected (Table 1). However, no such differences were found for CEM43°CT90.
Conclusion: The use of HT in combination with RCT is associated with good clinical outcome. Further analysis are required to assess the effect of temperature parameters on treatment outcome for specific indications.

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Mepitel Film vs standard treatment for preventing radiotherapy (RT) skin toxicity: phase III study

Type: Clinical

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Aims: Evidence supporting use of Mepitel Film for prophylaxis of radiation-induced skin toxicity is limited. We aimed to assess the feasibility and efficacy of Mepitel film for preventing breast skin toxicity (RTOG score) in two radiation oncology centres in Switzerland.
Methods: This was a phase III randomized controlled multicentre trial comparing Mepitel Film and standard local treatment (ST) for preventing skin toxicity in breast cancer patients, treated with postoperative radiotherapy.
Results: 161 patients were recruited between 2016 and 2020. Demographic characteristics of the two groups of patients were well balanced. 83.1% of patients were treated according to study protocol.

RTOG ≥1 score was 90.7% vs 94.9% and RTOG≥2 was 9.3% vs 13.9% (in Mepitel arm vs ST respectively).

RTOG toxicity≥1 was observed after median 26 days in Mepitel arm vs 21 days in ST arm ($p=0.0052$), with a reduction in median recovery times (19 vs 32 days) ($p=0.0068$).

Multivariate analysis, controlled for age, diabetes, BMI and smoking exposure, showed a 41% reduction in the risk of RTOG ≥1 (HR = 0.59 95% CI (0.42–0.84), $p=0.0036$.

In the Mepitel arm, the median time to evidence of RTOG≥2 was 51 days vs 57 ($p=0.0569$) and multivariate analysis showed a reduction in the risk of RTOG ≥2 of 71% (HR = 0.29 95% CI (0.09–0.92), $p=0.0357$.
Conclusion: The study showed overall improved toxicity control for the experimental arm, a reduction in the risk of toxicity and a reduction in recovery times.

Impact of recurrence frequency and pattern on survival and posttherapeutic outcome in patients with oral squamous cell carcinoma after adjuvant radio-(chemo-)therapy (aRT/RCT)

Type: Clinical

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Aims: A retrospective study aimed to analyze the treatment outcome of patients with primary oral cavity carcinoma that received initial curative adjuvant radio-(chemo-)therapy (using VMAT) at the University Hospital Basel between 2014 and 2019. The main focus was on recurrence-free survival and recurrence patterns. The therapy has been evaluated qualitatively in order to be able to draw conclusions on adjustments in the future.
Methods: All patients who had primary oral squamous cell carcinoma and received postoperative external beam radiotherapy during the initial curative treatment concept (adjuvant radio-(chemo-)therapy) between 2014 and 2019 were included. Data were obtained from the electronic medical records of the University Hospital Basel. To determine the mean radiation exposure towards radiosensitive tissues, the native CTs of all patients were contoured using "Velocity 4.1". Statistical analysis (Kaplan-Meier curves, Fisher's exact test) was performed by the Basel Institute for Clinical Epidemiology and Biostatistics using R version 4.1.2.
Results: A total of 25 fitting patients were found in the databases. Median follow up time was 746 days (range of 389–1248 days). Among these 25 patients, local recurrence occurred in 2 cases, regional recurrence in 1 case, and distant metastasis in 1 case. 1 patient developed both 1 local recurrence and 1 distant metastasis. All recurrences occurred in patients with a clinical/histopathological staging according to UICC of III or IVA. Recurrence-free survival 2 years after therapy was 91.1% (95% confidence interval: 80–100%) and overall survival was 100% (95% confidence interval: 100–100%). The most common adverse event encountered was xerostomia, accounting for 32.1% (chronic) and 60.1% (acute), respectively. >30% of patients had some kind of chronic side effects. Level 4 acute and/or chronic side effects were seen in 14.2% and 7.1% of patients, respectively.
Conclusion: Few local and regional tumor recurrences occurred in the patients enrolled after radical resection and postopRT/RCT. The severity of chronic side effects was moderate. This demonstrates a sufficient compromise of the intensity of postopRT/RCT.

Radiation dose on bone marrow correlates with acute hematotoxicity in patients with advanced cervical cancer

Type: Clinical

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Aims: For women with locoregionally advanced cervical cancer FIGO stage IIA–IVA, the current standard of care treatment is radiochemotherapy (RCT) combined with a sequential brachytherapy boost. The radiosensitivity of bone marrow (BM) precursor cells is high and there seems to be a connection between BM dose-volume histograms (DVHs) and acute hematotoxicity (HT). Hence a BM sparing radiation therapy could improve hemoglobin levels and overall survival (OS). Therefore, in this study a relationship between delivered radiation dose to BM and acute HT was investigated.
Material and Methods: A retrospective analysis of 31 patients (age 25–78 years) with FIGO stage IIB–IVB was performed. The patients were treated between 2010 and 2016 with definitive RCT at the department of Radiation Oncology at the Klinikum rechts der Isar in Munich. Bone structures such as pelvic bones (PB) and the femoral heads (FH) as the site of hematopoisesis were contoured and the resulting DVHs were correlated with white blood cells (WBC), hemoglobin levels and platelets.
Results: The data showed a significant correlation between WBC levels and the median dose, V5 Gy and V50 Gy of the left ($p=0.049$, $p=0.005$, $p=0.063$) and right FH ($p=0.025$, $p=0.004$ and $p=0.014$). Furthermore, significantly correlations between the grade of leukopenia and median dose, V30 Gy, V40 Gy and V50 Gy of the PB ($p=0.016$, $p=0.043$, $p=0.012$ $p=0.016$) existed. Correlating the grade of anemia with the PB, significant correlations in mean dose, maximum dose and V50 Gy ($p=0.015$, $p=0.029$, $p=0.034$) could be found. No correlation between the hemoglobin levels and both FHs were observed.

When correlating the amount of thrombopenia with the dose volumes of all three regions, there could only be found a significant correlation for V5 Gy of the right FH ($p=0.03$). There was no significant correlation between hemoglobin levels and OS as well as progression free survival (PFS) could not be found.
Conclusion: The results show that distinct dosimetric subvolumes in the femoral heads and the pelvis may correlate with blood levels and therefore have a potential impact on therapeutic outcome and treatment-related-toxicity.

Variations in contouring brain target volumes and Organs at Risk on 3 T vs. 7 T MRI: An intra-rater/inter-rater analysis study

Type: Clinical

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Aims: Low-grade gliomas account for around 2/3 of gliomas in young adults. The current standard of radiotherapy (RT) planning including delineation organs at risk (OAR) and target volumes is based on 1.5 or 3 T MRI (3 T MR).

To determine whether 7 T MRI (7 T MR), with its higher resolution, offers an advantage in RT planning, we investigated inter/intra-rater variation in segmentation of targets and OAR on 7 T MR compared to 3 T MR.
Methods: Ten patients with suspected low-grade glioma underwent non-contrast 3 T and 7 T MR before surgery. Images included T1, T2 and FLAIR sequences.

OAR and target volumes were delineated on both 3 T and 7 T MR images by three physicians experienced in central nervous system. Agreement between raters (inter-rater-variability) was measured by Dice coefficient (DC) which is a metric of volumetric overlap, and volumetric error. Additionally, the DC of each 3 T/7 T MR pair per rater was analyzed to assess intra-rater-variability.
Results: One thousand two hundred structures were examined. For GTV, the average DC was 0.84 (+/–0.19) at 3 T MR and 0.77 (+/–0.23) at 7 T MR. CTV DC was 0.89 (+/–0.07) at 3 T MR, as well as 0.85 (+/–0.1) at 7 T MR. The PTV values were 0.90 (+/–0.07) and 0.87 (+/–0.1) respectively.

Delineating CTV on 3 T and 7 T MR lasted 16:40 min (+/–0:09:39) and 13:23 min (+/–0:06:53), respectively. Mean size of PTV volumes were 274.6 cm^3 (+/–177.6) in 3 T MR and 256.1 cm^3 (+/–166.7) in 7 T MR.

Comparing 3 T MR/7 T MR intra-rater-variability, mean DC was 0.87 (+/–0.1) for target volumes and 0.63 (+/–0.18) for OAR.
Conclusion: Overall, while 7 T MR showed a trend towards shorter target volume contouring times and smaller target volumes than 3 T MR, it also showed a trend towards lower levels of agreement between raters. In intra-rater analysis, target volumes showed a good overlap, while OAR contouring demonstrates large differences, especially in peripheral OAR like optic structures.

Reasons of lower agreement on 7 T MR for most structures could be high sensitivity to motion, technically less homogeneity of imaging as well as limited clinical experience with 7 T MR based contouring.

Therapy resistance of glioma in relation to the subventricular zone: what is the role of radiotherapy?

Type: Clinical

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Aims: Glioma is a highly heterogeneous primary malignant brain tumor with marked inter-/intratumoral diversity engendering a dismal prognosis. It may contain a population of neural stem cells (NSC) and cancer stem cells (CSC) that have the ability of migration, self-renewal and differentiation. While both may contribute to therapy resistance, NSC may additionally play a role in brain tissue repair. The subventricular zone (SVZ) is the main reservoir of NSC.
Methods: This study investigated the impact of bilateral SVZ radiation dose on treatment outcome. We included 182 glioma patients. Tumors were classified based on their spatial relationship to the SVZ. SVZs were delineated and dose was extracted from dose volume histograms. Dose and outcome correlations were investigated with Cox regression and Kaplan-Meier analysis.
Results: Median progression free survival (PFS) was 8.8 months; median overall survival (OS) was 16.6 months. On the univariable analysis, patients with ipsilateral SVZ receiving ≥59 Gy showed significantly better median OS (18.9 vs 13.9 months; $p=0.014$). Furthermore, lower doses (10–46 Gy) to the contralateral SVZ were associated with improved median PFS (8.8 vs 2.8 months; $p=0.002$). Infiltration of SVZ found to be highly significant for decreased median PFS (7.9 vs 11.3 months; $p=0.013$) and OS (15.3 vs 20.9 months; $p=0.005$) on both univariable and multivariable analysis.
Conclusion: In this cohort, targeting the potential CSC in ipsilateral SVZ while sparing contralateral NSC correlated with an improved outcome. Further studies should address optimizing dose distribution with modern radiotherapy techniques for areas enclosing CSC and NSC.

Fast thermoradiation therapy: a new approach available at the Radiation Oncology Clinic, Oncology Institute of Southern Switzerland (IOSI)

Type: Clinical

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Aims: Thermoradiation therapy is the combined use of radiotherapy and hyperthermia (HT), which consists of heating of the tumour region up to 40–43 °C for one hour. HT enhances the efficacy of radiotherapy through the block of radiation-induced DNA repair, direct cytotoxicity of hypoxic cells and tissue reoxygenation. HT is effective if delivered within a short time interval (ideally <60 min) after irradiation. In order to quickly reach therapeutic temperatures, efficient technology and clinical workflow must be adopted.
Methods: In our institute, devices for both superficial and deep HT (ALBA hyperthermia, Med-Logix srl) are available. The HT treatment room is adjacent to the linac bunker to minimize the time interval between beam off and HT treatment start. Trained clinical staff facilitates patient positioning and superficial/intracavitary temperature measurement set up. Powerful radiofrequency generators and ergonomic water boluses allow efficient power deposition within the body, producing the fast heating up to therapeutic temperatures in 3–10 min.
Results: Since July 2021, more than 20 patients have been treated with fast thermoradiotherapy for superficial tumours such as recurrent breast cancer, carcinoma of the thoracic wall, skin melanoma, soft tissue sarcoma. Since December 2021, also the treatment of deep-seated tumours is feasible and patients with indications including recurrent anal or rectal cancer, bladder cancer, retroperitoneal liposarcoma were recruited. HT was generally well tolerated by patients and did not cause added toxicity. Our institute is currently joining different multicentre clinical studies within Switzerland and Europe.
Conclusion: Fast thermoradiation therapy is feasible and its efficacy is being confirmed by the preliminary clinical results, showing no added toxicity and promising outcomes. Clinical studies will aim at demonstrating thermoradiation therapy efficacy and suggesting its application in earlier tumour stages.

MRI guidance for thermoradiation therapy: planning and verifying the treatment

Type: Clinical

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Aims: Thermoradiation therapy (HTRT), i.e., the combined use of radiotherapy and hyperthermia (HT), can benefit from image guidance to improve treatment precision and personalization. In our institute, the presence of a deep HT device (ALBA 4D, Med-Logix) and a 1.5T scanner for Magnetic Resonance Imaging (MRI, Philips Ambition X-RT) in the same room allows easy access to imaging for patients undergoing HT. Thanks to this feature, different scientific projects involving MRI in HTRT treatments are being started, as described in this contribution.
Methods: MRI will be exploited for three main tasks: i) study of electrical and ii) thermal properties of tissues, which are required for accurate estimation of temperature distribution during HT planning, and iii) treatment outcome quantification. For the first task, MRI sequences highlighting the water content, which largely contributes to the electromagnetic properties of tissues, will be investigated as a wide-spectrum alternative to electrical property tomography. For the second task, tissue vascularization and oxygenation will be described through dedicated MRI sequences (e.g., DIXON, diffusion-weighted, and dynamic contrast-enhanced MRI). For the third task, MRI will be used for diagnosis and tumor grading, supporting patient stratification and personalized treatment.
Results: As already stated in the literature, the patient-specific characterization of electrical and thermal tissue properties will lead to more accurate HT treatment planning, which is pivotal for safe and effective treatment. Moreover, the quantification of HTRT efficacy through MRI will provide unquestionable clinical evidence to define new approaches to tumor treatment.
Conclusion: The availability of an MRI scanner in the HT treatment room enables MRI guidance in HTRT, paving the way for the development of new strategies to plan and verify the treatment and allowing our institution to offer the best treatment quality to patients.

Assessment the accuracy and precision of the Verathon Bladder scan i10® in men receiving radical, adjuvant or salvage radiotherapy for prostate cancer

Type: Clinical

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Aims: About 5–10% of men undergoing radiotherapy for prostate cancer (PC) suffer from radiation cystitis. Adequate bladder filling during CT simulation and treatment results in less exposure to radiation, potentially reducing acute and late side effects. Bladder scanners could be used to verify bladder filling in order to avoid additional dose from repeat imaging and improve patient comfort. The aim of our study was therefore to evaluate the accuracy of the Verathon BladderScan i10®.
Methods: 16 consecutive patients with PC undergoing radical, adjuvant or salvage radiotherapy were selected. Bladder volumes measured with the Verathon Bladder Scan were compared with volumes estimated in the CT or CBCT scans. 27 pairs of data were collected. Bland-Altman plot and Lin's correlation concordance coefficient were used to evaluate the accuracy and precision of the Bladder scan i10®. The results were compared with the contouring inter-operator variability. The bladder was contoured on 16 images by a radiation oncologist, a medical dosimetrist and a radiotherapy technologist. For each image, the standard deviation of the bladder volumes was calculated. Inter-operator variability was estimated as the mean value of the standard deviations.
Results: The image-based bladder volumes ranged from 83 to 364 ml. The Bland-Altman plot showed a mean difference of –8.6 ml (accuracy) of the BladderScan i10® measurements, with variability ranging from –61.1 to 44.0 ml (95% limits of agreement). The differences were independent of the bladder volume. The results were confirmed by the Lin's concordance correlation coefficient that showed bias correction factor Cb = 0.99 (high accuracy) and Pearson correlation coefficient $\rho = 0.95$ (moderate precision).The inter-operator variability was 10.7 ml (1 standard deviation), while the precision of the bladder scan was 26.8 ml (1 standard deviation). The larger range of variability of the measurements could be due to the bladder wall volume that is included in the images but not in the scanner measurements.
Conclusion: The Verathon BladderScan i10® is suitable to predict adequate bladder filling before CT simulation or radiotherapy treatment.

Whole brain radiation therapy for patients with brain metastases: survival outcomes and prognostic factors in a contemporary institutional series

Type: Clinical

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Aims: To study survival outcomes and prognostic factors in patients undergoing whole brain radiation therapy (WBRT) for brain metastases in the contemporary setting.
Methods: Patients undergoing WBRT from 2013–2021 in our department were retrospectively included in an ethics-approved institutional database. Patient demographics and clinical parameters were collected from electronic medical records. Patient and treatment characteristics included factors such as patient age, primary tumor histology, karnofsky performance status (KPS), extracranial tumor burden, as well as WBRT dose and fractionation. Overall survival (OS) was calculated from onset of WBRT using the Kaplan Meier method. Statistical analyses were performed using RStudio (Boston, USA).
Results: At the time of submission, 222 patients have been included, of which 92 (41%) and 130 (59%) were male and female, respectively. Patients were a median of 63 years (range, 29–85) old at time of WBRT. The most common tumor entity was non-small cell lung cancer (39%), followed by breast cancer (22%), small cell lung cancer (15%) and melanoma (9%). Median follow-up was 4.0 months (range, 0.2–106.8). Median OS for the entire cohort was 4.8 months (95%-CI, 3.5–7.0). OS differed between histologies ($p = 0.04$), with the longest survival seen in patients with breast cancer (median 7.0 months; 95%CI 3.9–10.1). Patients with KPS ≥70 survived for a median of 6.9 months (95%CI, 4.8–8.1), compared to 1.7 months (95%CI, 1.2–2.6) in patients with KPS <70 ($p < 0.01$). Patients receiving WBRT doses of ≥30 Gy survived longer than those receiving <30 Gy (median 8.0 vs. 2.2 months; $p < 0.01$), although the former also had higher KPS scores ($p < 0.01$). No OS difference was seen between patients aged ≤60 and >60 years ($p = 0.28$). Additional analyses in an updated cohort will be presented at the conference.
Conclusion: Survival outcomes of patients undergoing WBRT in the contemporary era appear overall comparable to historical cohorts. Prognostic factors are valuable to guide treatment decisions in the palliative setting.

Late-onset toxicities after definitive radiochemotherapy of nasopharyngeal Carcinoma–a monocentric analysis

Type: Clinical

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Aims: The definitive radiochemotherapy (RCT) is the therapy of choice for nasopharyngeal carcinoma (NPC). The aim of this monocentric retrospective analysis was to record predominately the late-onset toxicities (LOT) with respect to their quality and quantity in order to deduce recommendations for the treatment planning and supportive therapy.
Methods: Compilation and analysis of all analogue and digital files from our departments of Otorhinolaryngology and Radiation Oncology as well as information from the Munich Cancer Registry. Inclusion Criteria for patients: Histologically proven NPC treated by definitive RCT with a minimun follow-up (FU) after RCT-Start of 6 months. From 1990–2018 73 patients (51 men, 22 women) could be included. Most recent collection of data: 15.12.2021. Average FU period: 76 (median: 63 [6–290]) months. Average age: 52 (median: 52 [20–85]) years. UICC-Stadium: 1×I; 11×II; 23×III; 35×IVA; 3×IVB. Histology: 31×squamous; 5×adeno; 5×undifferentiated; 30×lymphoepithelial; 2×unknown. RT-technique: 26×2D/3D; 47×IMRT/SIB-IMRT. Average first maximum dose.: 2.1 Gy; average total maximum dose: 68.2 Gy; average duration of RT: 47.4 days. Graduation of Toxicity according to CTCAE v.5.0.

Results: Disorders of the pituitary-thyroid axis were the most common with 18/73 patients. Disorders of the hypothalamus-pituitary-adrenal axis (HPA) were in 2/73 cases acutely life-threatening. There was a need for surgical intervention, especially in the late toxicity from the ENT spectrum such as sinusitis, mastoiditis and otitis. In addition to the late toxicity mentioned, acute Wernicke encephalopathies (WE) occurred in two cases. These occurred an average of 67 days after the start of the RCT and must therefore be classified as early-onset toxicities.
Conclusions: Due to the risk of WE it is advisable to determine vitamin levels and substitute at an early stage, especially if there is a risk of malnutrition such as pronounced acute radiogenic dysphagia or parenteral nutrition. Electrolytes should be checked regularly as a prophylactic measure. In the event of a sudden electrolyte imbalance, careful investigation must be initiated.

Exclusive intra operative radiotherapy with the Xoft Axxent®: preliminary results of the Oncology Institute of Southern Switzerland

Type: Clinical

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Aims: The aim of the analysis is to report the feasibility and the in-breast recurrence rate in early breast cancer patients treated with exclusive intraoperative radiotherapy with 50-kV orthovoltage X-rays.
Methods: From January 2019 to May 2022 52 patients have been treated with the Xoft Axxent® electronic brachytherapy system, 20 Gy single-fraction, as exclusive partial breast irradiation.

Patients were eligible, according with ASTRO and GEC-ESTRO guidelines, if aged>60 years and treated for ductal and other favourable histologies, unifocal, positive receptor status, pT1 pN0 (sentinel node), grade 1–2, R0, luminal A.

The treatment was feasible when the distance from the surface of the applicator and the skin was > 1 cm. A lead shield has been positioned between the breast gland and the pectoralis muscle for avoiding inappropriate dose to chest wall.
Results: The mean tumour size was 1 (0.4–1.9) cm, the diameter of the balloon device was 3–4 cm in 80% (42/52) of the patients, the median and mean applicator volume were 35 and 39 cc, the median and mean irradiation time were 9.2 and 8.3 min.

At the definitive histological examination 3 patients resulted with a lobular carcinoma and 3 with a multifocal tumour. At a median follow-up of 15.6 (0.6–38.9) months, 1 in breast relapse was observed.

1 patient died for non-breast cancer reasons, 2 patients developed other cancers and 1 patient developed bone metastasis.

No patients was referred to external radiotherapy or chemotherapy.

7/52 (13%) patients developed a not complicated seroma in the tumour bed.

45/52 (86.5%) patients had a good cosmetic result.
Conclusion: Our experience showed that the Xoft Axxent® system is safe and its use is friendly as reported by the personnel involved.

The acute and late toxicity were moderate, we diagnosed seroma in 13% of cases, decreasing over time.

As reported in literature the adequate patient's selection is the milestone for the outcome of the intraoperative radiotherapy.

Nevertheless a longer follow up is needed to evaluate adequately the outcome: until now our unique relapse occurred after two years from the treatment.

Retrospective single center data regarding low dose radiotherapy for benign diseases

Type: Clinical

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Aims: A descriptive evaluation of our experience of low dose radiation therapy for benign diseases. These data represent an important basis for further planning of prospective studies in radiation therapy and an analysis of the workload involved.
Methods: Retrospective single center analysis from 08/2014 to 01/2021 of the indication for radiation of benign diseases according to DEGRO S2 guidelines. Our center has two orthovoltage radiation therapy machines and three linear accelerators.
Results: A total of 1451 patients with benign diseases were irradiated (13% of all irradiated patients) and 2455 courses of radiotherapy were performed, 747 (30.4%) on the linear accelerator and 1708 (69.6%) on the orthovoltage radiotherapy machines. The mean total radiation dose for the painful osteoarthritis of the small and large joints was 6 × 0.5 Gy = 3 Gy (0.5–8 Gy). The mean age of the patients was 62 years old (range 19–94 years old), 1000 (68%) patients were women and 451 (32%) men. The most common indications for low dose radiotherapy were: finger osteoarthritis 383 (26.3%), plantar fasciitis 214 (16.6%), gonarthrosis 174 (11.9%), epicondylitis radialis humeri 123 (8.4%) and achilles tendinitis 104 (7%). 55% of the patients received only one course of radiation, due to the good response.
Conclusion: This analysis of clinical data provides a valuable overview of the indications for low dose radiotherapy in patients with benign diseases treated at the Radiation Oncology Center KSA-KSB over a six-year period. In-depth retrospective evaluations are in progress.

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Intermediate outcomes of moderate hypofractionated adjuvant whole breast RT with simultaneous integrated boost

Type: Clinical

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Aims: We report treatment outcomes up to 3-years for patients who received adjuvant moderate hypofractionated whole breast radiother-

apy with simultaneous integrated boost (SIB-mhWBRT) following breast-conserving surgery.
Methods: SIB-mhWBRT for breast cancer patients was introduced in our department in 07/2017. This prospective study includes 424 patients treated with SIB-mhWBRT for stage I–III invasive breast cancer ($n=391$) and/or ductal carcinoma in situ (DCIS, $n=33$) until 12/2021. Mean patients age was 60 (range, 27–88) years. Mean/median follow-up was 23/25 (range, 1–54) months. SIB-mhWBRT was applied with 40 Gy in 15 daily fractions over 3 weeks according to the START B trial, with a SIB dose to the tumor bed of 48 Gy delivered as 3D conformal RT ($n=402$), intensity-modulated RT ($n=4$) or volumetric-modulated arc therapy ($n=18$). Since 05/2018 patients indicating for lymphatic pathway RT were also included ($n=62$). Follow-up data including objective assessment of baseline parameters and treatment-related outcomes, in addition, subjective patient reported outcome measures (PROMs) was recorded and reported.
Results: Acute toxicity grade 0/1/2/3 was in 24.2/62.5/13/0.3% at the completion of RT. The only patient with grade 3 (bleeding) presented this symptom already postoperatively, before start of RT. Data of 267/250/209/106 patients was available for 6-months/1/2/3-year follow-up. Grade 2 and higher complications were identified in 11.6/7.2/5.3/2.9% at 6 month/1/2/3 years.

PROMs cosmesis results were evaluated as excellent-good/fair/poor in 97/2.4/0.6% at 6 months; in 96.3/3.3/0.4% at 1 year; in 96.8/2.7/0.5% at 2 years; in 97.5/2.5/0% at 3 years post RT, respectively.

For patients with invasive breast cancer the 3-year overall/cancer specific/disease-free survival was 97.7/98.5/95.2%. 3-year risk of any locoregional recurrency was 0.7%. No mortality or relapse was observed in DCIS patients.
Conclusion: SIB-mhWBRT demonstrated very favorable side effect profiles and cosmesis/PROMS. 3-year results demonstrate excellent locoregional control.This short-term regimen offers substantial patient comfort and improves institutional efficacy.

A feasibility trial of preoperative radiosurgery for resectable brain metastases (PREOP-1)

Type: Clinical

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Aims: Retrospective reports of preoperative radiosurgery for brain metastases describe high efficacy with minimal toxicity[1]. We present an interim analysis of a feasibility trial of radiosurgery prior to neurosurgical resection of a brain metastasis.
Methods: Eligibility criteria included: a brain metastasis up to 4 cm in diameter and up to three other brain metastases for radiosurgery, anticipated gross tumour resection, an estimated prognosis of at least six months and no contraindication to steroids or MRI. The date for elective neurosurgical resection was set following the tumour board and single fraction radiosurgery could be delivered up to the day of surgery.
Results: Twelve patients of median age 65 years (41–77) were recruited between 11/2020 and 02/2022. 3/12 had synchronous brain metastases. 7 had a single metastasis, 4 had two, and 1 had three brain metastases. 11/12 patients received preoperative radiosurgery and metastasectomy as intended. The twelfth patient went directly to surgery and received postoperative fractionated stereotactic radiotherapy (fSRT). The median time between referral and radiosurgery was 5.5 working days (1–10) and neurosurgery took place a median of 1 day later (0–5), thus the median time from tumour board to metastasectomy was 7.5 working days (2–10). The median encompassing dose was 16 Gy (14–19), median GTV was 9.6 cm^3 (7.0–21.5) and median PTV was 12.7 cm^3 (5.9–26.1). 2/11 patients have completed 12 month follow-up without local recurrence or leptomeningeal disease. There was one acute related toxicity (grade 2 alopecia) at 3 months which recovered by 6 months, and six patients have died from extracranial causes. The patient who received postoperative SRT developed two small leptomeningeal metastases 3 months later.
Conclusion: Preoperative SRS was feasible in 11/12 patients and safe in 11/11 patients. This protocol constitutes the experimental arm of a randomised trial to compare the efficacy of preoperative radiosurgery against postoperative hypofractionated stereotactic radiotherapy (PREOP-2).

[1]Prabhu RS et al. Preoperative Radiosurgery for Resected Brain Metastases, IJROBP 2021

The influence of image guidance on patterns of failure after IMRT for head and neck cancer–A systematic review.

Type: Clinical

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Aims: IMRT is considered standard of care for head and neck squamous cell carcinoma (HNSCC). Improved conformity over older techniques has led to concerns of increased rates of marginal failures. Correct target volume definition and low residual patient setup uncertainty are crucial to avoid geographical misses. While patterns of failure (PoF) after IMRT for HNSCC have been published before, the role and influence of image guidance (IGRT) is unclear. This work provides a systematic review of the consideration of IGRT in PoF studies after IMRT for HNSCC.
Methods: A systematic literature search according to PRISMA guidelines was performed on PubMed for HNSCC, IMRT and PoF terms and conference abstracts from ESTRO and ASTRO 2020 and 2021 were screened. Entries were de-duplicated and cross-reference validation was performed. Studies were included if they related PoF of HNSCC after IMRT to the treated volumes. Data on IGRT, treatment adaptation, PoF and correlation of PoF to IGRT was extracted.
Results: 95 studies were included. The majority (60) did not report any information on IGRT. The remainder reported daily IGRT (15), daily on day 1–3 or 5, then weekly (4), weekly (11), or other schemes (5). Immobilization was performed with masks (71 studies), non-invasive head frames (4), or not reported (20). PoFs only either on CT, MRI or PET-CT were reported in 12 studies with the remainder mixing multiple modalities. The most common PoF classification was "in-field/marginal/out-of-field", reported by 60 studies with 35 studies utilizing a multitude of other classifications.

Plan robustness was addressed in 8/95 studies. Only one study correlated PoF on MRI images to IGRT on 106 non-metastatic nasopharyngeal cancer patients. 15 patients suffered 21 failures, 10 of which were in-field, 9 marginal and 2 out-of-field. Identified causes were subopti-

mal target definition or coverage, long overall treatment time and, for one patient, a high frequency (20%) of setup displacements >3 mm.
Conclusion: Only one PoF study correlated patterns to IGRT measures and setup uncertainty. More data on this topic is direly needed. A prospective trial examining the influence of IGRT on PoF is planned.

Postmarketing usability evaluation of intra-uterine brachytherapy applicators–implications on quality and safety

Type: Clinical

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Aims: Usability research looks at an interaction between human operators and medical devices. Therefore, usability testing is an important aspect that should ideally be conducted on anyone who interacts with the device, from physicians to technical staff responsible for sterilizing or preparing the device. The conceptual foundation of usability evaluation is rooted in Human-Centered Design (HCD). Usability assessments involve several qualitative and quantitative methods.
Methods: Our brachytherapy (BT) unit uses a selection of different BT applicators, two of which were used for this analysis: device number 1) Venezia Applicator (Elekta AB, Stockholm, Sweden), device number 2) Geneva Applicator (Elekta AB, Stockholm, Sweden). First, we adapted the usability questionnaire for quantitative data collection proposed by Parreira et al. for this study [1]. The adapted questionnaire consists of 27 items on a 7-point Likert scale (from 1–totally disagree to 7–totally agree) suitable for our clinical environment. Second, we informed members of our BT team of the project's goal. Third, the printed questionnaire was handed out together with written instructions and filled out by participants. Statistical analysis was done by calculating Cronbach's alpha and item-domain correlation for internal consistency.
Results: Fourteen members of our brachytherapy team answered the questionary (five physicians, three radiation therapists, two medical physicists, three nurses, and one nurse assistant). The internal consistency of the 27-items usability questionnaire was $\alpha = 0.93$ for Venezia Applicator, and $\alpha = 0.93$ for Geneva Applicator and the item-total correlation values were also good (all above 0.30). The average usability score for Venezia Applicator and Geneva Applicator was 5.81 and 5.41 respectively (range: 1 to 7).
Conclusion: Preliminary results indicate an excellent internal consistency of the questionnaire. The overall usability of the devices was satisfactory. Usability testing provides actionable insights for the team.

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Tolerance of adjuvant ultra-hypofractionated whole breast radiotherapy–a single institution analysis

Type: Clinical

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Aims: This single-institutional, prospective analysis evaluated early and intermediate time treatment tolerance in patients who underwent adjuvant ultra-hypofractionated whole breast radiotherapy (uhWBRT) after breast-conserving surgery.
Methods: uhWBRT was introduced in our department in 03/2020. This study evaluated acute and intermediate time side effects. Till 02/2022, 189 consecutive patients with breast tumors without indication for lymphatic pathway irradiation were included in this analysis: 158 with invasive carcinomas (pT1: 110, pT2: 46, pT3: 2), 31 with DCIS. Mean age was 60 years (range, 26–89), mean/median follow-up (FU) was 9/10 (0–23) months.

Acute reactions were accessed at completion of RT and after 2–3 weeks. Intermediate time side effects and patient reported outcome measures (PROMs) were evaluated 6 mo. after RT and in yearly interval afterwards, respectively.

Prescribed dose was 26 or 28 Gy in 5 fractions (F) to the whole breast and 10–12 Gy in 4–5 F applied as a consecutive hypofractionated boost (hB) in 102/158 patients.

Mean treatment time was 1.9 (1–3) weeks.
Results: Acute toxicity grade 0/1/2/3 was observed in 28/61/11/0% at RT completion. 2–3 weeks after RT, toxicity profile shifted towards lower skin reactions with 44.5%/49.7%/5.8% grade 0/1/2. 6 mo. FU ($n = 141$) demonstrated fibrosis grade 0/1/2 in 77.3%/19.9%/2.8% and pigmentation changes grade 0/1 in 79.4%/20.6%. Breast edema grade 0/1/2 identified in 80.9%/16.3%/2.8%. 3.5% of patients were seeking medical intervention (eg. physiotherapy). 6 months PROMs cosmesis was evaluated in 52.5%/43.3%/4.3% as excellent/good/fair. 1-year FU results ($n = 100$) were comparable: fibrosis grade 0/1/2 in 79%/18%/3%, skin telangiectasia grade 0/1 in 99%/1%, pigmentation changes grade 0/1 in 85%/15% and breast edema grade 0/1/2 in 78%/18%/4%. 1 yr. PROMs cosmesis was stated excellent/good/fair in 54%/42%/4%.
Conclusion: We found high subjective and objective early and intermediate time treatment tolerance following uhWBRT +/–hB. Patients are very satisfied with short treatment time and cosmesis. In addition, the regimen provided substantial increase in department capacity which was critical during COVID19 pandemic.

Prognostic Biomarkers in Head and Neck Squamous Cell Carcinoma Treated with Radiotherapy–A Systematic Review

Type: Clinical

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Purpose: In recent years, an increasing numbers of biomarkers has come into use in oncology. However, few personalized treatments exist for head and neck squamous cell carcinoma (HNSCC), so far. To summarize available evidence, we performed a systematic review of biomarkers in HNSCC treated with curative-intent radiotherapy (RT).
Methods: We searched Pubmed and EMBASE for literature on biomarkers in HNSCC. Inclusion criteria: 1) HNSCC, 2) ≥ 10 patients, 3) association with relevant oncological endpoint, 4a) all patients treated with RT or 4b) separate outcome reported for RT-treated patients, 5) publication between Jan 2010 and Feb 2022. Exclusion criteria: 1) biomarker was change in HPV/EBV-DNA, 2) HPV-status as biomarker for outcome, 3) studies solely based on public databases (TCGA, NCDB), 4) reviews. Z curves were generated to analyze publication bias. OncoKB was used to identify potentially druggable targets.
Results: We screened 5005 publications and excluded 4870 based on in-/exclusion criteria, leaving 135 for data extraction. The most common primary tumor sites were oropharynx (46.1%), larynx (18.1%) and oral cavity (17.1%). 11.7% were early AJCC/UICC stage (I–II), whereas 81.5% were advanced stage (III–IV), data was missing for 6.8%. Median minimum prescribed equivalent dose 2 Gy was 66 (14–72) Gy. The most common biomarkers were proteins (38.9%), DNA (14.4%) and mRNA (9.0%). Limiting analysis to prospective data and statistically significant results, we found three potentially druggable targets: ERCC2, PTCH1 and EGFR. Data quality was limited: AJCC/UICC version was not provided in 60.7% of studies and stage was missing in 31.8%. For 34.0% of biomarkers, only univariable analysis of outcome was available.

72.5% of publications were retrospective studies, 7.2% prospective randomized trials and 2.2% prospective, non-randomized trials. Z-curves indicated the presence of publication bias.
Conclusion: There is an abundance of reported biomarkers in HNSCC but data quality is limited due to retrospective collection, univariable testing, lack of validation and publication bias. Potentially druggable biomarkers are available and should be further explored.

Patterns of failure after image-guided brachytherapy: a retrospective swiss cervical cancer cohort study

Type: Clinical

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Aims: The standard of care for advanced cervical cancer is concomitant chemoradiotherapy followed by brachytherapy. Image guided adapted brachytherapy (IGABT) allows dose escalation to the primary high-risk target volume while sparing organs at risk. This is a report on clinical outcome and patterns of failure in a multi-institutional cohort study.
Methods: From 11 institutions in Switzerland patients were treated with chemoradiation and referred to Bern University Hospital for IGABT with magnetic resonance imaging (MRI) or computed tomography (CT) guidance. The pattern of failure at time of first relapse was analyzed. Kaplan-Meier estimates at 3 years were calculated for local control (LC), recurrence free survival (RFS) and overall survival (OS).
Results: 132 patients referred for IGABT were treated between 2010–2018. In 119 of these patients data was available for recurrence analysis. Median follow up was 26 months (mean 35 months), percent of patients per FIGO 2014 stage IA/IB/IIA 32.2%, IIB 31.4%, IIIA-IVB 35.6%. 82.9% had squamous cell carcinoma; 72.9% lymph node involvement at diagnosis. EBRT dose was prescribed according to institutional guidelines; 93.1% received concurrent chemotherapy.

44 failures occurred in 33 of 119 patients (27.7%). Among the 44 failures, 36.4% were loco-regional (25.0% local, 11.4% regional) and 63.6% distant. Of the patients with treatment failure, 18.2% had pelvic failure alone, 63.4% had distant failure alone (paraaortic or systemic), and 18.2% had both pelvic and distant failure. Failure occurred 69.7% in the first year, with a further 18.2% in the second year.

The 3-year LC, RFS and OS were 87.9%, 49.36%, 60.7%.
Conclusion: Implementation of state-of-the-art IGABT combined with modern radio-chemotherapy leads to favorable local and loco-regional control and has shifted the patterns of relapse for cervical cancer. Predominance of systemic failure, as seen in larger cohorts in the literature, is confirmed in our cohort.

A semantically interoperable framework for locoregionally advanced cervical cancer data management

Type: Clinical

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Aims: Structured data collection is a prerequisite for cost-efficient and effective quality assurance and research. In this work, we report the design process for institutional data collection based on the SmartOncology platform.
Methods: We created a list of clinically significant variables mirroring the most important prognostic and predictive factors in cervical cancer. Additionally, we developed core data set for reporting radiation therapy treatment-related data. We base the selection of variables on clinical experience, literature research, and clinical guidelines. For every variable, we have searched clinical terminology servers (Unified Medical Language System) and coding systems to develop controlled vocabulary.

Finally, we implemented a data capture graphical user interface and data exchange interfaces in SmartOncology–an open-source system for clinical data management and vocabulary development.
Results: Four clinicians were engaged in the development. We invested 45 working hours in developing vocabularies and data entry interfaces. As a result, we selected 87 (100%) clinical and therapy-related parameters in the final list. In addition, we identify standardized terms and codes for 40 (47%) parameters. For 46 (53%), we adopted internal standard nomenclature and definitions. The distribution of data types was as follows: codable concept–54 (63%), date–18 (21%), base unit–7 (8%), and derived unit–7(8%). We will submit all data points definitions and codes to the Basic Register of Thesauri, Ontologies & Classifications (https://bartoc.org/).
Conclusion: Developing resources for structured, semantically interoperable data capture within a clinical environment is feasible, cost-effective, and efficient. We are continuing implementation in other radiation oncology domains.

Myelopathy after radiation for a spinal metastasis in a patient being treated with tyrosine kinase inhibitor Vandetanib mimicking spinal progression

Type: Clinical

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Aim: We report a case of a radiation necrosis 1 year after radiation therapy in a patient radiated for a spinal metastasis of a medullary thyroid carcinoma and under Vandetanib therapy.
Methods: The medullary thyroid carcinoma was initially treated in 2001 by surgery. In 2015 the patient was diagnosed by a DOPA-PETCT with multiple metastases. In 02/2016 therapy with Vandetanib was started. Due to multiple bone metastases associated with pain, radiotherapy was given to T5, T9-10 and the right acetabulum with 12 × 3 Gy = 36 Gy in 09/2020. Due to progression, Vandetanib was changed to Selpercatinib 02/2021. In 11/2021, one year after radiotherapy, the patient reported sensory disturbances in the legs. Physical examination showed hyperreflection of both lower extremities, dysesthesia at the right leg and weakness in the left leg. A MRI showed a lesion in the spinal cord at level T5, interpreted as progression. A DOPA-PETCT showed no uptake, thus, a radiation necrosis was assumed.

Treatment with Bevacizumab resulted in neurologic improvement of the initial symptoms and an MRI showed a stationary lesion in the spinal cord at level T5. At the last follow up, the patient had residual symptoms with clinically a bilateral paraparesis with emphasis on the left side.
Results: The palliative radiation dose given in this case results very rarely in a myelopathy. There are no reported cases of radiation myelopathy after the treatment with this dose. We suppose that the tyrosine kinase inhibitor Vandenatinib plays a role in the development of this complication. In literature, Vandetanib has been considered as a radiosensitizer, for example in treating liver tumors or head and neck tumors combined with radiation, thus, this combination being the possible cause of radiation necrosis in our patient.
Conclusion: To our knowledge, this is the first case report on myelitis with low dose radiation combined with Vandenatinib. Caution has to be taken when tyrokinase inhibitors are combined with radiation, especially in patients treated by multiple targeted agents who can achieve long survival as possible interaction/sensitization in tissue reactions of the spinal cord is not known.

Clinical quality assurance in image guided brachytherapy of cervix cancer

Type: Clinical

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Aims: Image guided adaptive BT (IGABT) in the context of chemo-radiation (ChRT) improves outcomes when compared with conventional BT of cervical cancer. IGABT implementation requires technological upgrading, process adaptation and personnel training. Systematic clinical oversight is needed for its safe and effective utilisation, but recommendations on this topic are lacking. We aimed to develop and test a clinical quality assurance (cQA) system for cervix cancer ChRT/IGABT.
Materials and Methods: We identified treatment parameters with established prognostic impact on the outcome of cervical cancer ChRT/IGABT. For each parameter, an evidence-based threshold was determined, indicating the minimal proportion of patients in whom a certain condition should be met for optimal outcome. Based on this framework and the GEC ESTRO-ICRU 89 Report, we developed a system for routine recording and automated reporting of parameters. The system was tested on the first 4 consecutive cervical cancer patients treated with ChRT/IGABT at our department.
Results: We established 17 key performance indicators (KPIs) and a minimal required set of 6 dose-volume checkpoints for patient-specific cQA. KPIs were selected to probe 4 domains of treatment overall ChRT schedule, IGABT procedure, doses to organs at risk and doses to target volumes. Patient-specific checkpoints were designed to track the total reference air kerma (TRAK) and relation between the D90 for high-risk clinical target volume and D2cc for rectum, bladder, sigmoid colon, bowel, and vagina. The automated reporting system was proven feasible for routine clinical use.
Conclusion: Our cQA system enables standardized, automated and evidence-based oversight of ChRT/IGABT, realtime treatment adaptations, literature-benchmarking and continuous streamlining of clinical pathways. The system has been proven feasible and was implemented in routine clinical practice at our department.

Chemoradiation as an effective treatment option in secondary, locally advanced leiomyosarcoma of the bladder after successful treatment of retinoblastoma during childhood

Type: Clinical

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Aims: Leiomyosarcoma (LM) of the bladder is a rare disease representing less than 1% of the tumors of the bladder. The primary treatment is surgery. In a locally advanced or metastasized situation prognosis is poor.

In children with Retinblastoma (RB) a secondary tumor can occur with a risk of 20%, being the first cause of death of RB survivors.

Hereby, we present a patient with a secondary LM of the bladder after successful treatment of bilateral RB during early childhood.
Methods: A 47-year-old male patient who suffered from a bilateral retinoblastoma at age 3, which was then successfully treated with enucleation of the right eye and radiotherapy (RT) of the left eye, was diagnosed with a locally advanced, inoperable LM of the bladder in 01/2020. Due to the local situation and suspicion of a solitary bone metastases of the pelvis, 6 cycles of chemotherapy with Adriblastin and Holoxan were administered and surgical options should be re-evaluated. In 07/2020 MRI pelvis showed stable disease. Chemotherapy was continued with Cisplatin/Gemcitabine. In 12/2020 liver metastases were diagnosed and palliative systemic treatment with Trabectedin was implemented. In 07/2021 imaging showed an increase of metastases and local tumor progression. Therefore, systemic treatment was changed to Atezolizumab, unfortunately with poor response. Due to

further progression of the primary tumor with increasing local symptoms a palliative concomitant chemoradiation (RCT) was performed in 11/2021. The patient received 18 × 2.75 Gy = 49.50 Gy in RapidArc technique with 6 MV photons and Adriamycin weekly.
Results: In 02/2022 CT scans showed a good response of the primary tumor and substantial relief in local symptoms. Unfortunately, it also showed a systemic progression of the disease, including liver, lung, soft tissue and bone metastases. Further systemic treatment was continued with Pazopanib.
Conclusion: Due to the rarity of the cases, there are no published data regarding the option of RCT in inoperable LM of the bladder. In this specific patient a good response to treatment could be achieved. Therefore, RCT should be considered a possible approach in locally advanced stages.

Dose escalation to 54 Gy in rectal adenocarcinoma patients is sufficient to obtain clinical complete response and avoid surgical management

Type: Clinical

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Aims: Locally advanced rectal cancer is treated with radiochemotherapy combined with adjuvant surgery. Total neoadjuvant treatment (TNT) and dose escalation trials have shown improved clinical outcome and a pathological complete response (pCR) rate≈30%. The aim of our study is to evaluate the impact of dose escalation up to 54 Gy on pCR
Methods: Radiation therapy was delivered using IMRT in two phases: 45 Gy in 25 fractions to the rectum and pelvic nodes with a simultaneous integrated boost (SIB) of 50 Gy to the rectum followed by a sequential boost of 4 Gy in 2 fractions of 2 Gy delivered to gross disease. Target volumes were defined as per RTOG guidelines. Dose constraints were applied: sigmoid Dmax < 54 Gy, bowel V40 Gy < 200 cm^3, cauda equina Dmax < 50 Gy.
Results: Three patients received dose escalated radiotherapy up to 54 Gy. All patients received concurrent capecitabin. One patient received TNT with 5 cycles of consolidation FOLFOX. The first phase of radiation was delivered on our linear accelerator Versa HD (Elekta) and the sequential boost was delivered on our MRI linear accelerator Unity (Elekta). All aforementioned dose constraints were respected. 95% of the dose was delivered to at least 98% of the volume as per institution guidelines. Treatment tolerance was comparable to standard rectal irradiation: patients presented G1-2 dermatitis, G1-2 gastrointestinal toxicity and no or little urinary toxicity. Patients underwent rectoscopy, MRI and PET restaging on average 54, 58 and 68 days after radiation treatment, respectively. One patient had a radiologic complete reponse, 2 patients had near radiologic complete reponse.

Rectoscopy showed pCR for all patients. Four months after radiation, all patients continue oncologic follow up and none have required surgical resection.
Conclusion: Increasing the dose to gross disease to 54 Gy seems sufficient to produce pCR in rectal adenocarcinoma without increasing toxicity. This allows patients to benefit from a watch and wait attitude, avoiding the need for a potentially morbid rectal surgery.

Combined hyperthermia and radiotherapy in patients with symptomatic tumor compressions

Type: Clinical

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Aims: Hyperthermia (HT) is an evidence-based radiosensitizer and has been shown to provide clinical benefits in the setting of re-irradiation and palliative cases with advanced metastases and symptomatic tumor compressions (STC). We evaluated the effects and quality of life (QoL) of combined hyperthermia and radiotherapy (HTRT) in these patients.
Methods: We retrospectively analyzed the overall survival (OS), local progression-free survival (LPFS) of patients with STC treated with HTRT between 2017 and 2021. Additionally, a QoL analysis was performed via EORTC QLQ-C30 quality of life questionnaires (version 3.0) at baseline, end of treatment, 3 months and 12 months.
Results: Altogether, 43 SC patients treated with HTRT were identified. Of these, 14 received a radiation dose ≥ 50 Gy (range 50–76 Gy, mean 56.4 Gy) and 29 received a dose < 50 Gy (range 12.5–49 Gy, mean 35.6 Gy). The patients received a median number of 6 HT sessions (range 1–10, mean 5.5). After a median follow-up time of 12 months (range 3–46), the median OS was 16.3 months in the <50 Gy group and was not reached in the group receiving ≥50 Gy. The median LPFS was 8.8 months in the <50 Gy group and not reached in the group receiving ≥50 Gy($p = 0.04$). The QoL analysis showed very favorable results for HTRT with no visible decline in EORTC QLQ-C30 functional, symptom or global health status scales at the end of treatment, 3-month and 12-month follow up compared to the baseline analysis at treatment start.
Conclusions: Combined HTRT was effective in patients with advanced metastases und STC. The outcome was superior in the group receiving ≥50 Gy with no visible decline in the EORTC QLQ-C30 quality of life analysis. These results support the use of HTRT in these patients who often have very limited treatment options and also supports individualization of the RT dose.

First results of the Swiss VENUS SHELL study: Time to pre-position and comfort for breast prone positioning using 3d-printed personalized shells

Type: Clinical

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Aims: The VENUS SHELL trial (Validating pErsoNalized 3D-printed Unique breaSt SHELLs) is a proof-of-concept study investigating time, comfort and positioning accuracy of personalized breast immobilization shells for breast prone radiotherapy (RT). We report a first analysis of the time to pre-position and the patient's reported comfort.

Methods: We enrolled patients aged 18 or more with a WHO performance status ≤2 who were scheduled to undergo adjuvant RT after a breast-conserving surgery or mastectomy for breast cancer. Exclusion criteria were: known cutaneous allergies to medical plasters or plastic substances; body weight >90 kg; current pregnancy; or had a mastectomy without breast reconstruction.

A personalized shell was produced based on a body-surface scan and 6 ultra-low dose CT scans were acquired on the prone board, 3 with and 3 without shell. The time needed to position the patient before each CT was recorded. Patients filled out comfort surveys after the surface scan and the CT imaging session.

Results: We enrolled 15 left and 5 right-sided breast cancer patients. Median age (range) was 59 years (41–80), breast cup size ranged from A to G and median body-mass-index was 24 (17–32). No significant difference was detected ($P=0.24$) for the pre-positioning time (1.8 ± 0.6 min with shell and 2.0 ± 0.8 without). The surface scan experience was rated positively with a median rating of 6 out of 7 (5–7). 85% of patients reported a comfortable position with the shell against 45% without.

Furthermore, they reported less pain ($P=0.005$), a less unpleasant experience ($P=0.01$) and less urge to move ($P=0.03$). Patients with cup-size ≥ D ($n=5$) reported a reduced or absent pressure on the contra-lateral breast when using the shell.

Conclusion: These results show that using Venus shell™ it is possible to position the patient prone in less than 2 min in a comfortable position that reduces the urge to move, confirming results from an interim analysis (10/20 patients). The positioning accuracy will be investigated next to verify if the millimetric pre-positioning accuracy seen in the first 10 patients is also confirmed.

Long term preservation of leg function after treatment of a large melanoma metastasis by short course radiation therapy with concomitant hyperthermia

Type: Clinical

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Aims: The management of advanced melanoma remains a major challenge and consists predominantly of systemic therapy. External beam radiotherapy (RT) has a role in palliation and hyperthermia (HT) combined with RT is a proven radiosensitiser in melanoma [1].

Materials and Methods: A 71 year old male patient, ECOG 0, (first diagnosis nodular melanoma of the left thigh, initially pT3a pN3 cM0, Stage IIIc, Clark level IV, Breslow 2.8 mm in 2010), presented in April 2013 with a large metastasis (max. diameter 14.5 cm) on the left lower leg (PET-CT 01.03.2013). The metastasis developed after 16 months Zelboraf/Vemurafenib and after multiple surgeries. At the interdisciplinary tumor board, HT with concurrent RT was recommended to avoid amputation. The patient received 36 Gy (6×6 Gy) photon irradiation to the metastasis (Fig. 1) combined with twice weekly superficial hyperthermia (Fig. 2: BSD 500, Spiral-8 applicator 915 MHz/max. power 136 W). A maximum temperature of 42–42.5 °C for 60 min was recorded using non-invasive thermometry.

Results: Combined HTRT was well tolerated with an acute dermatitis (CTC v5 grade 3). PET-CTs following RTHT showed an impressive response (Fig. 3+4). The patient subsequently received immunotherapy with pembrolizumab for further metastases. 9 years after completion of the thermoradiotherapy there is no residual tumor currently and the patient is fully active without any functional limitations.

Conclusion: This case illustrates the excellent efficacy of thermoradiotherapy without relevant late toxicity and indicates a great treatment potential in melanoma.

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Real-time intrafraction prostate motion monitoring and management during dose-escalated prostate cancer Stereotactic Body Radiation Therapy (SBRT)

Type: Clinical

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Background: SBRT requires tight planning margins, high dose gradients, and strict adherence to planning criteria in terms of patient positioning and organ motion management. We report the first Swiss clinical experience with an innovative electromagnetic (EM) tracking device for intrafraction prostate motion monitoring and management during dose-escalated linac-based SBRT for prostate cancer (PCa).

Methods: 13 patients received prostate SBRT using flattening filter-free (FFF) volumetric modulated arc therapy (VMAT) for a primary ($n=9$) or an intraprostatic recurrent PCa ($n=4$) (01.2022–06.2022). The EM tracking device consists of a Foley catheter with an integrated transmitter. Setup accuracy was verified with a Cone-Beam CT (CBCT) matching. Motion was monitored in the 3 directions during all the procedure. Treatment was manually interrupted when the signals exceeded a 2 mm threshold in any of the three spatial directions. A new CBCT was performed if the offset was transient (>20 secs.).

Results: All the patients completed the planned treatment. In 1/65 fractions was not possible to deliver the treatment because of an excessive displacement, but the fraction was successfully delivered the day after. Prostate was out of the tolerance in 13.8%, 9.9% and 6.18% of the total treatment time in the vertical, longitudinal and lateral directions, respectively. Prostate showed a motion pattern predominantly in the vertical direction, and whatever the considered distance displacement: 47.5%, 13.8% and 4.8% for displacements of, respectively, >1 mm, >2 mm and >3 mm.

Conclusions: For the fist time in Switzerland, EM-based, real-time motion monitoring was successfully implemented in our department for prostate SBRT. Our results showed that, using this system, a 2 mm CTV-PTV margin could be safely applied. We found a small number of fractions with motion exceeding the predefined 2 mm threshold, which would have otherwise gone undetected without intrafraction motion monitoring.

Real-time intrafraction prostate motion monitoring and management during dose-escalated prostate cancer Stereotactic Body Radiation Therapy (SBRT): early clinical evaluation.

Type: Clinical

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Aims: We report the first Swiss early clinical experience with an innovative electromagnetic (EM) tracking device for intrafraction prostate motion monitoring and management during dose-escalated linac-based SBRT for prostate cancer (PCa).
Methods: 10 patients received a LINAC-based prostate SBRT with the following schedule delivered over 5 consecutive fraction, using a SIB technique (01.2022–06.2022):

- Prostate + 2 mm: 36.25 Gy
- Dominant intraprostatic lesion (MRI-based) + 2 mm: 40 Gy

The EM tracking device consisted of a Foley catheter with an integrated transmitter. Patients were simulated and treated with a filled bladder and an empty rectum. We verified setup accuracy with a CBCT. Motion was verified during all the procedure. Treatment was manually interrupted when displacements were >2 mm in any of the three directions.
Results: Median age was 75.6 years (range: 70.4–84.6); 2, 4, 2 and 2 patients were classified as ISUP 1, 2, 3 and 4, respectively. Three patients received androgen deprivation therapy during SBRT. All patients received the planned treatment. Prostate was out of the tolerance margins in 15.1%, 10.6% and 6.4% in the vertical, longitudinal and lateral direction, respectively. The motion pattern was predominantly in the vertical direction with 46.6%, 15.1% and 4.6% of the displacements >1 mm, >2 mm and >3 mm, respectively.

Two patients presented a G2 urinary toxicity ($n=1$) or a G2 rectal toxicity ($n=1$), disappeared in the 7 days after SBRT with anti-inflammatory drugs. 3 patients had a follow-up visit 4 months after the end of SBRT, without any reported toxicity. All the patients presented a median biochemical response after SBRT of 75% (range: 43–100), except one patient presenting a PSA bounce 1 month after SBRT, with a PSE normalization 3 months later.
Conclusions: We successfully implemented EM real-time gating for dose-escalated prostate SBRT. Very early clinical data and compliance are encouraging. Longer follow-up is needed and is ongoing.

Risk of bleeding following robotic stereotactic body radiation therapy in patients with localized prostate cancer in patients receiving baseline anticoagulant or antiplatelet therapy

Type: Clinical

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Aim: This retrospective study aims to evaluate the rates of hematuria and hematochezia following robotic stereotactic body radiotherapy (rSBRT) in localized prostate cancer receiving baseline anticoagulation and/or antiplatelet therapy.
Methods: Localized prostate cancer patients treated with rSBRT between 2015–2021 on at least one anticoagulant/antiplatelet medication at baseline were included.

Hematuria and hematochezia were scored using the CTCAE v4. Cystoscopy and rectoscopy findings were retrospectively reviewed when available.
Results: Thirty-two men with a median age of 72 years (Range: 56–85) with a history of taking at least one anticoagulant and/or antiplatelet medication were treated using rSBRT (CyberKnife; Accuray Inc., Sunnyvale, CA, USA). rSBRT was delivered in 5 fractions to a dose of 35 Gy or 36.25 Gy every second day. Median follow-up was 30 months (Range: 12–60). Nineteen patients (60%) received antiplatelet medications (Aspirin+/– Clopidogrel) while 7 (22%) used direct oral anticoagulants (DOAC) and 6 patients (18%) were on warfarin.

Overall, 4 patients (12%) experienced hematuria (Grade 2 or lower) with a median time of 13 months post-SBRT. Of these patients, 3 (75%) received Aspirin +/– Clopidogrel, and 1 (25%) warfarin. Bleeding was self-limiting and patients did not undergo any invasive procedures. Hematochezia occurred in 4 patients (12%) with grade 2 or lower and in one patient (3%) with grade 3 at a median time of 5 months post-SBRT. Four (80%) of these patients were on Aspirin +/– Clopidogrel and 1 (20%) on DOAC. Three patients underwent rectoscopy for diagnostic purposes. Two patients had hemorrhoids and one patient had radiogenic proctitis and underwent intervention to stop the bleeding.
Conclusion: In this single institution cohort, low-grade GI & GU bleeding was observed in patients receiving platelet aggregation inhibition (Aspirin/Clopidogrel). High-grade bleeding was rare. Baseline anticoagulation usage might be considered as a risk factor for GI/GU bleeding following prostate rSBRT but not as a contraindication.

Biochemical control after robotic stereotactic body radiation therapy for unfavorable intermediate and high-risk prostate cancer: a single institutional experience with mid-term follow-up

Type: Clinical

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Aim: To retrospectively assess the biochemical outcome and pattern of recurrence of unfavorable intermediate-risk (IR) and high-risk (HR) prostate cancer (PC) patients treated with robotic stereotactic body radiotherapy (rSBRT).
Methods: We evaluated patients with unfavorable IR- and HR-PC treated from January 2015–June 2021 with rSBRT (CyberKnife; Accuray Inc., Sunnyvale, CA, USA) with or without androgen deprivation therapy (ADT). Biochemical Relapse Free Survival (bRFS) was assessed using the Phoenix nadir +2 definition and measured using the Kaplan-Meier method. Acute and late genitourinary (GU) and gastrointesteinal (GI) toxicity were assessed using Common Terminology Criteria for Adverse Events (CTCAE) v.4.0
Results: Forty patients (24 unfavorable IR and 16 HR according to D'Amico Criteria) with a median age of 71 years (range 52–85 years) and median initial PSA of 9.3 ng/ml (3–41 ng/ml). About 25% of patients had cT3a/b disease. rSBRT was delivered in 5 fractions to a dose

of 35–36.25 Gy prescribed to the 80% isodose. About 52.5% of patients received ADT with a median duration of 6 months (6–24 months). At a median follow up of 30 months (range: 12–84 months), four patients developed biochemical recurrence, resulting in a 3-year bRFS rate of 91.5%. Three patients had biopsy-proven local failure and 1 patient had radiological evidence of regional lymph node metastasis. Two patients (5%) had grade-3 acute, and 1 patient (2.5%) grade-3 late GU toxicity. There were no grade 4/5 toxicities.
Conclusion: At median follow up of 30 months, favorable bRFS was observed after rSBRT for unfavorable intermediate and high-risk prostate cancer with low GU- and GI-toxicity profile.

Development of applicator prototypes for cervix cancer brachytherapy using the EMBRACE 2 optimization objectives for the target volume and organs at risk

Type: Clinical

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Aims: Previously, we reported on analysis of target volume coverage by the applicators for cervix cancer brachytherapy (Radiother Oncol 2010;96(1):70). Here we expand the study to complex intracavitary/interstitial prototypes, adding the organs at risk dose to optimization criteria.
Materials and methods: Brachytherapy target volumes of 264 cervix cancer patients from 3 centres were registered to reference tandem & ring, resulting in a virtual patient (VP) in DICOM format, containing pooled information from all patients. Iso-Density Envelopes (IDE) of the VP were created and labelled according to proportion of encompassed VP. Residual volume at risk (RVR) around each IDEn% was generated and divided into RVRn%Bladder, RVRn%Rectum, RVRn%Sigmoid, and RVRn%Bowel. Universal intracavitary/interstitial (IC/IS) applicator to treat the VP was created through optimization iterations. Dose was optimized with IC and universal IC+/IS applicator according to EMBRACE II aims for 13 IDEn%/RVRn% (5%-steps from IDE50%/RVR50%-IDE95%/RVR95% and 1%-steps from IDE98%/RVR98%-IDE100%/RVR100%).
Results: Universal IC/IS prototype consists of a tandem & ring with channels for IS needles in three planes. Source positions in the needles parallel to the tandem serve as the ring channel, which is omitted. Needles planes 2 and 3 are oblique. IC optimization achieved hard constraints for the target up to IDE65% at a minor cost of RVR violation. Beyond IDE65%, IC optimization became increasingly limited with a sharp drop from IDE80%/RVR80%. Across the VP, IC+IS optimization achieved higher target parameters, while RVRn%dose was comparable to IC optimization. This advantage was relevant up to IDE98%/RVR98% and was not accompanied by a higher total reference air kerma relative to IC technique. At ≥IDE99%/RVR99%, IC+IS optimization was unable to meet the IDE aims despite RVR violation.
Conclusions: Universal IC+IS prototype demonstrates favorable characteristics according to EMBRACE 2 planning aims for the target and organs at risk. We hypothesize it may be adequate for treatment of >95% of clinical cases. Alternative techniques may be needed in the remaining unfavorable tumors.

Which patients need more resources in Proton Therapy? Analysis of need for replanning and recalculation at the Paul Scherrer Institute

Type: Clinical

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Aims: Proton therapy (PT) allows a very conformal treatment and a significant decrease of the dose delivered to the non-target tissue because of its remarkable physical property. However, uncertainties and inaccuracies that affect the dose distribution are to be avoided in particular with this highly conformal technique.

This study evaluates the need for plan recalculation and replanning for patients undergoing PT at the Paul Scherrer Institute (PSI), reasoned by medical issues, difficult positioning or anatomical changes during treatment course.
Methods: From 01.09.2021 to 31.10.2021, 45 patients were treated on our two gantries (33% of the yearly gantry workload) with Pencil Beam Scanning PT. All patients were evaluated in terms of the three different treatment issues affecting the dose distributions: 1) Medical reasons (i. e. pain, dysphagia, nausea), 2) Anatomical changes (i. e. shape, tumor response, cavity filling) or 3) Positioning changes (i. e. residual rotations, obesity, kyphoscoliosis). These patients were marked as challenging. The prevalence of recalculation and/or re-planning arising from these reasons, have been evaluated for both gantries, bearing in mind that one patients could have several issues.
Results: On Gantry 2, 8/18 (44%) patients were defined as challenging patients due to medical ($n=4$), anatomical ($n=4$) and/or positioning ($n=5$) issues, whilst on Gantry 3, 14/27 (52%) patients were challenging ($n=8$ medical, $n=7$ anatomical and/or $n=5$ due to positioning issues). Recalculations were performed on 21 different plans for 14/18 (78%) patients in Gantry 2, resulting in 6 replannings for 6/18 (33%) patients.

For Gantry 3, 18 recalculations were performed for 10/27 (37%) patients, of which 8 replannings were performed for 6/27 (22%) patients.
Conclusion: The rate of plan recalculation and replanning at PSI is currently significant and plays a relevant role in our daily management of patients. In particular, some patients need more than one of these procedures during the treatment course. In order to predict the need for these time consuming processes, a score is currently being developed including the medical, anatomical and positioning aspects.

Combined hyperthermia and radiotherapy in patients with advanced sarcomas

Type: Clinical

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Aims: Hyperthermia (HT) is an evidence-based radiosensitizer and is reimbursed in Switzerland in combination with radiotherapy (RT) for treatment of advanced sarcomas, chordomas and desmoid tumors (SCD). Aim of this study was to evaluate the effects of combined hyperthermia and radiotherapy (HTRT) on overall survival (OS) and local progression-free survival (LPFS) in these patients.
Methods: All patients with SCD treated with deep-tissue HTRT between 2011 and 2021 were retrospectively analyzed
Results: Altogether, 39 SCD patients treated with HTRT were identified. Of these, 23 patients received a radiation dose of 50 Gy, four patients received 30 Gy and 12 patients received 70 Gy. The patients had a median number of 6 HT sessions (range 1–10, mean 6.5). After a median follow-up time of 12 months (range 1–121 months), the median OS was 5.6 months in the 30 Gy-group, 16.5 months in the 50 Gy-group and wasnot reached in the 70 Gy-group, resulting in a statistically significant difference in the logrank comparison ($p=0.001$). In comparison, the median LPFS was not reached in any of the groups and showed no significant difference. A total of 9 patients were treated with palliative intent (PI), while the remaining 30 patients were treated with curative intent (CI). CI-patients had a significantly longer median OS (53 months) and LPFS (not reached) compared to only 12 months (OS) and 20 months (LPFS) in patients treated with PI ($p=0.001$, respectively). Patients treated with 50 Gy had differential outcomes depending on whether they received surgery or not.

Patients with surgery presented a significantly better median OS (41 months) and LPFS (not reached) compared to only 12 months (OS, $p=0.03$) and 13 months (LPFS, $p=0.004$) in the no surgery group.
Conclusions: Combined HTRT was effective in patients with advanced SCD. The outcome was superior in the group receiving a definitive radiation dose of 70 Gy, patients receiving surgery after 50 Gy, as well as patients treated with curative intent. These results support the use of HTRT in this cohort of patients with advanced tumors and also supports individualization of treatment.

Outcome of salvage radiotherapy after radical prostatectomy for patients with biochemical failure and negative PSMA PET-CT scan

Type: Clinical

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Aims: To retrospectively assess oncological outcomes and report pattern of recurrence of prostate cancer patients treated with salvage radiotherapy (SRT) for biochemical failure with no evidence of disease based on prostate specific membrane antigen positron-emission tomography (PSMA PET) after radical prostatectomy (RP).
Methods: This retrospective, multicenter analysis included patients who underwent SRT following RP due to biochemical failure with no evidence of disease on PSMA-PET scan. Biochemical recurrence-free survival (bRFS) and clinical progression-free-survival (cPFS) were generated using Kaplan-Meier method. Multivariable Cox proportional hazards regression assessed predictors of survival outcomes.
Results: Out of 379 identified patients, the majority (84.2%) received SRT exclusively to the prostate bed while in 15.8% elective pelvic nodal irradiation was considered. Only 16.9% received concomitant androgen deprivation therapy (ADT). Median follow-up after SRT was 33 months (IQR: 20–46). The 3- and 5-year bRFS following SRT were 70.3 and 42.3%, respectively. Using univariate analysis, a Gleason score of higher than 7a ($p=0.003$), seminal vesicle infiltration ($p=0.001$) and a higher pre SRT PSA level (>0.2 ng/ml) ($p=0.028$) were significantly associated with a worser bRFS.

On multivariable Cox proportional hazards, all previous factors remain negative predictors for biochemical failure. Following SRT, nodal relapse, predominantly within the pelvis, was the most common pattern of recurrence (22 patients out of 48) followed by bone metastasis (15 out of 48).
Conclusion: In this multicenter retrospective study, using PSMA PET as state of the art in staging patients with biochemical recurrence, the oncological outcomes of SRT to the prostate bed +/– pelvic nodes remain in-line with literature without significant improvement.

Case series of reirradiation of isolated local recurrent prostate cancer using 1.5 T MR-Guided and daily adapted salvage SBRT.

Type: Clinical

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Aims: To evaluate the feasibility of Salvage Stereotactic Body Radiotherapy (re-SBRT) using the Elekta 1.5T MRI linear accelerator (Linac), delivered to the prostatic bed for local recurrence, in 4 patients previously irradiated for prostate cancer.
Methods: 4 patients received re-SBRT between January 2020 and June 2022. All patients had clinical/radiological local relapse in the prostatic bed and no distant metastasis. The age of patients varies from 66 to 78 year-old. They were treated by radical prostatectomy and had salvage external beam radiotherapy of the prostatic bed (70 Gy) for biochemical recurrence. Before re-SBRT, the average PSA level increases was 3.64 ng/ml. We offer a re-SBRT on the recurrence in the vesiculo-prostatic bed (VPB) proven by PSMA PET-CT. Considering the re-irradiation, dose constraints were V25 Gy < 0.03cc for the rectum, V27 Gy < 5cc for the bladder and V25 Gy < 10cc, V35 Gy < 0.03cc for bowels. We pay attention to not overpass a maximum ($EQD2/\alpha/\beta=3$ Gy) given to the rectum, bowels and bladder of 100 Gy.

SBRT plan was computed with Monaco treatment planning system. We report dosimetric parameters and toxicity (CTCAE) at 3 months for 4 patients and at 6, 9, 12, 18 and 24 months for 2 patients, after SBRT completion.
Results: The selection of the total dose for salvage-SBRT(5×5, 5×6, or 6×6 Gy) delivered to the VPB hypermetabolic volume was based on dose-limiting toxicity. Median fraction time was 31 min. Daily dosimetric readaptation was done, according to MRI imaging in real time. Median Maximum Cumulative dose given to the rectum was 92.97 Gyeq. The followup was 24 months for 2 patients and 3 months for the others 2 patients. Neither of the 4 cases experienced acute or chronic GI toxicity nor acute GU toxicity. Chronic GU toxicity was a maximum Grade 2 for only one patient, requiring medical management and disappearing 3 months later.
Conclusion: No standard local treatment exists for patients with a local recurrence after a prostatic bed radiotherapy. SBRT in re-irradiation setting using the MRI-Linac system with daily dosimetric adaptation, appears as a promising tool without major urologic or rectal complications.

Clinical feasibility of breast tumor bed irradiation with the 1.5 T MR-linac

Type: Clinical

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Introduction: The Hybrid magnetic resonance linear accelerator (MR-Linac) has the potential to test novel concepts in breast cancer patients such as a better visualisation of the tumor bed, organs at risks and the possibility to adapt the treatment plan online. Interactions of secondary electrons within the magnetic field in particular air electron stream effect (ESE) and the electron return effect (ERE) have to be considered.
Aim: Assess clinical feasibility of breast tumor bed irradiation (BTBI) in 2 patients with the Elekta 1.5T MR-Linac.
Methods: 73 and 70 years-old women, affected respectively by unifocal carcinoma NST of the left breast pT1b pN0 M0 G1 and micro-invasif carcinoma of the right breast pT1mi pN0 M0 G3, treated by lumpectomy and sentinel lymph node biopsy. A boost on the tumor bed was performed due to close margins<2 mm and the G3 respectively for patient 1 and 2. The clips had migrated and the tumor bed was not visible on the planning CT.

42.4 Gy in 16 fractions was delivered with a VERSA-HD accelerator linac and the boost of 10.6 Gy in 4 fractions on tumor bed with the MR-linac.

Dose-volume constraints for planning Whole-Breast hypofractionated radiotherapy was assessed according to the RTOG 1005 criteria.

In vivo dosimetry was performed using TLD placed on the one patient's chin and results were compared with the dose simulated by the treatment planning system (TPS).
Results: BTBI using the 1.5 T MR-Linac was successfully performed with a 7 MV photon with IMRT step-and-shoot plan using a TPS Monaco. The MRI guided radiotherapy allows better visibility of the tumor bed. Daily dosimetric readaptation was done, according to MRI imaging in real time.

The treatment was well tolerated, patients developed a slight acute toxicity, i. e. breast skin erythema and breast oedema for one patient CTCAE grade 1.

ESE and dose from ERE was low and not associated with an increased risk of acute toxicity.
Conclusion: Improving the visibility of tumor bed reduce the volume of breast tissue irradiated and therefore the risk of late treatment-related-toxicity. This should open up prospects for partial breast irradiation in selected patients with this novel technology.

Radiotherapy-associated changes in saliva composition: a systematic review

Type: Clinical

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Aims: We aimed to review the existing data and provide an overview of saliva changes in patients receiving radiotherapy (RT) to the head and neck region. To our knowledge, this is the first systematic review assessing the fluctuations in saliva pH, its buffering capacity as well as electrolyte concentrations during and after RT.
Methods: Two reviewers independently searched the PubMed, Cochrane and Embase databases for studies published in English between 1980 and 2022 analyzing the saliva composition of patients at several time points before, during and after RT to the head and neck region or comparing saliva results to a healthy control group.
Results: Of 1312 publications screened with the search term "saliva AND radiotherapy", 66 met the eligibility criteria. There is a large variety of RT settings, its techniques as well as time points and methods of saliva collection in the literature.

Salivary pH changes and buffering capacity were examined in 27 and 11 studies, respectively, with a substantial decrease in values described in most of the studies (Table 1) during and post-RT. Ten studies depicted the fluctuations in electrolyte concentration (natrium, potassium, chloride, calcium and others) (Table 1). The majority of those studies showed an initial elevation of natrium followed by a decrease during and post-RT, and reduced concentrations for potassium and magnesium post-treatment.
Conclusion: Radiation-associated saliva alteration manifests in a substantial decrease in pH/buffering capacity and change of electrolytes.

Type: Physics

A simple and precise isodose-based dose verification method for HDR brachytherapy plans

Type: Physics

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Aims: Like in EBRT, an independent treatment time calculation should be performed also in HDR brachytherapy. We implemented an isodose-based verification method that can derive the integral dwell time very simple and precisely from the volume of an isodose of interest.
Methods: We used the planning system "Brachyvision" (Eclipse, Version 16.1.4, Varian). The Brachyvision dose calculations are based on the TG-43 method as established by the Task Group 43 of the AAPM. The irradiation plans are valid for a Gammamed Plus iX afterloading system (Varian) equipped with a nominal 10 Ci Ir-192 source.

Based on the calculated dose distribution around an Ir-192 point source up to a 15 cm radius, the following relationship was obtained:

$T = (30.05 \times V2/3 + 4.83 \times 10–4 \times V5/3)$ x D/A

T[s]: integral dwell time; V[cm3]: volume of the investigated isodose belonging to the dose D [Gy]; A [Ci]: (constant) nominal source activity of the Ir-192-source.

The first expression in the bracket reflects the d2 law, whereas the second expression accounts for absorption and scattering processes. Since D and A will be generally constant, the formula can be easily tabulated.

For verification of this method, we analyzed 18 HDR brachytherapy plans with various irradiation techniques (gynecological afterloading using cylinder applicators, interstitial brachytherapy and intraoperative radiotherapy (IORT) using rectangular flaps). T was considered to be

the integral dwell time, whereas V was the volume of the corresponding isodose comprising all dwell positions in the plan.
Results: The estimated integral dwell times generally matched for better than 2.5% with the integral dwell times obtained from Brachyvision. However, it should be noted that the shape of the evaluated isodose is comparable to a sphere and its diameter is below the 15 cm radius mentioned above.
Conclusion: The Isodose-based verification method is simple and accurate in independently verifying most HDR brachytherapy plans. The implementation in any modern brachytherapy planning system should be easy.

Evaluation of accuracy of various auto-segmentation tools for automatic delineation of target volumes in breast cancer irradiation

Type: Physics

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Aims: Automation of tasks by artificial intelligence (AI) is becoming in regular use in many fields with a significant impact in health care. The advent of computer vision in AI has enabled computers to segment and classify distinct objects within medical images, such as computer tomography (CT) scans. Auto-segmentation of CT images promises many benefits–such as faster and more standardized delineation of organs at risk or target structures. However, there are many providers of auto-segmentation software and their validity has not yet been sufficiently evaluated. Therefore we decided to compare the accuracy of auto-segmentation tools from various providers with manual contours created by radiation oncologists. We chose 11 patient data sets for our department that included standardized contours that have undergone external peer review.
Methods: Automatically delineated target volumes of breast treatments were created, which included the breast CTV, Axilla levels I–IV, intra-pectoral muscles and the internal mammary nodes. The volume of overlap between the oncologist delineated PTV and the automatically generated contour were calculated, as well as the total volume of both contours. This allowed us to calculate the similarity coefficient using the Jaccard index (overlap volume/total volume). For all delineated volumes we have generated treatment plans using standardized dose objectives and constraints in order to minimize the inter-planner variability.
Results: The results showed quite uniform similarity coefficients for most providers, averaging at around 70% to 80% similarity between auto-segmentation and the control contours. The largest discrepancy occurred when the patients had undergone mastectomy and the automatic systems could not recognize the thoracic wall, thus underestimating the required CTV volume. Treatment plans were compared using dosimetric parameters, plan robustness and complexity indices.
Conclusion: The small dose differences due various auto-segmentation tools highlight the potential to reduce the delineation time of breast CTV and corresponding lymph node levels.

Calculation of institution-specific safety margins in frameless mask-based image-guided stereotactic intracranial radiosurgery and radiotherapy.

Type: Physics

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Aims: To calculate institution-specific safety margins in frameless image-guided stereotactic intracranial radiosurgery and radiotherapy (SRS/SRT) delivered with the Accuray CyberKnife 6D skull tracking (6DST).
Methods: Institution data of 23 6DST End-to-End phantom-tests (E2E) and 91 6DST SRS/SRT clinical fractions (Fx) of 49 treatment plans (mean 2 Fx/plan, range 1–5) was used in this analysis. Margins were calculated using van Herk's recipe. MRI-CT images registration and GTV delineation errors were used from literature.

Prescription isodose was in the range of 70–80%. Penumbra width σp was determined from clinical plans. Plans were delivered with fixed aperture conical collimators. Each Fx data was considered to consist of minifractions (mFx) between consecutive image acquisitions and tracking correlations. Intrafraction targeting error (TE) is defined as difference between targeting coordinates of each pair of consecutive mFx.
Results: Mean E2E errors ± 1 SD were 0.13 ± 0.26, 0.19 ± 0.17, -0.09 ± 0.14 mm in Superior-Inferior (SI), Right-Left (RL), Anterior-Posterior (AP) directions, respectively. RMS of E2E errors were 0.28, 0.25, 0.16 mm (SI, RL, AP). For 49 plans 15,088 radiation beams within 6251 mFx of 91 Fx were analyzed. Mean time interval between consecutive images was 32 s (range 20–60 s). Mean TEs ± 1 SD were 0.00 ± 0.06, 0.00 ± 0.09, 0.00 ± 0.09 mm (SI, RL, AP) and 0.00 ± 0.12, 0.00 ± 0.10, 0.00 ± 0.05 degrees for yaw, pitch, roll rotations, respectively. RMS of TEs standard deviations of all Fx combined were 0.07, 0.10, 0.10 mm (SI, RL, AP). SD of GTV delineation/MRI-CT registration error was assumed 0.29, 0.28, 0.3/0.57, 0.33, 0.32 mm (SI, RL, AP). σp estimated as 3.60 mm. CyberKnife 6DST safety margin without GTV delineation and MRI-CT registration errors was calculated as 0.7, 0.6, 0.4 mm and overall margin as 1.8, 1.3, 1.2 mm (SI, RL, AP).
Conclusion: Institution-specific anisotropic safety margins required to ensure optimal target coverage in patient population was determined for 6DST delivery. Analysis demonstrated gross influence of GTV delineation and image registration errors to overall safety margin, therefore reduction of these should allow margin decrease.

Commissioning of synthetic CT images for dose calculation in MR-Only prostate radiotherapy treatment planning

Type: Physics

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Aims: Radiotherapy treatment planning based only on magnetic resonance imaging relies on synthetic Computed Tomography (sCT) images for dose calculation. A calibration curve is required for the con-

version of the Hounsfield Units into mass density values. This work shows the validation for dose calculation of the Philips MRCAT Pelvis® synthetic CT applied to prostate cancer treatments, to ensure dose consistency with the workflow based on CT scans.
Methods: Thirty-nine patients underwent both Magnetic Resonance (MR) and CT scans in the treatment position. VMAT plans with two full arcs were created on the planning CT (pCT) using the Varian Eclipse® planning system (v16.1). MR and CT images were rigidly co-registered and the treatment plan was copied on the sCT. The AcurosXB algorithm was used for dose calculation.

To estimate a custom density calibration curve from the Hounsfield Unit differences, a voxel-by-voxel correlation curve between the sCT and the pCT images was calculated using 19 patient data. Validation was carried out on 20 different patients. The calibration curve provided by Philips, the curve of the pCT and the custom curve were used for dose calculation on the sCT. The mean PTV and CTV dose was compared with the values calculated on the pCT.

The dose variation due to errors independent of the calibration curve was evaluated by setting the patient body of both image sets to homogeneous water density.
Results: Dose differences, independent of the calibration curve, were about 0.2% for both the PTV and CTV. Dose differences between the plans calculated on the sCT and on the pCT should reflect that distribution.

The Philips density curve overestimated the mean PTV and CTV dose by 1.2%. The dose difference achieved with the CT curve was 0.2% on the PTV and –0.02% on the CTV. Using the custom density curve the dose difference was 0.4% and 0.2% for the PTV and CTV.

Paired Wilcoxon test showed that only the dose differences with the custom density curve were not statistically different from the dose variations independent of the calibration curve.
Conclusion: The Philips calibration curve was not appropriate. The evaluation of a custom curve is suggested.

RapidPlan models for prostate radiotherapy treatment planning with 10 MV photon beams

Type: Physics

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Aims: The RapidPlan is a radiotherapy planning tool that uses a dataset of approved plans to predict the dose distribution and automatically generate the dose-volume constraints for optimization of the new plan This study compares three strategies of model building for the treatment of prostate cancer with the 10 MV photon beam.
Methods: Three models for prostate treatment has been compared: Model 6X, Model10X and Model6Xrefined. Model6X is already used in our department and it was trained on 6 MV photon beam plans. Model10X was created on 10 MV photon beam plans manually optimized by an experienced medical physicist.

Finally, Model6Xrefined was trained on plans automatically created by the Model6X, but using the 10 MV photon beam. The three models were used to generate 25 new plans with the 10 MV photon beam.
Results: Model10X generated plans with 2 Gy lower mean dose to Bladder-PTV and Rectum-PTV volumes and 8% lower V15 Gy at Bladder and Rectum volumes, although the number of monitor units increased by 170 on average.
Conclusions: The model trained on manually optimized plans generated plans with higher normal tissue sparing. However, model building is a time-consuming process so a cost-benefit balance should be performed.

Influence of autoplanning for plans optimised on manual- and automated-based delineation of normal structures for breast treatment.

Type: Physics

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Aim: to investigate the dosimetric impact of autoplanning for a cohort of early breast cancer patients for which OARs were delineated both on manual and automated basis.
Methods: Fifteen SIB left-breast patients under DIBH were involved. OARs including ipsi- and contra-lateral lungs, contra-lateral breast (CLB), heart and LAD were manually and automatically contoured. 60 and 50 Gy were prescribed to manually contoured PTVs. Automated plans were generated by means of a model trained with 80 patients previously referred to our institution. Manual plans were designed according to our internal optimisation template. Plans shared the same VMAT irradiation technique. Four plans were designed for each patient: MoMs, MoAs, AoMs, AoAs (Mo/Ao = Manual/Automated optimisation, Ms/As = Manual/Automated segmentation). Dosimetric differences between Mo- and Ao-based plans were carried out ensuring the same PTVs coverage. Dosimetric differences between MoMs and MoAs (ΔM) as well as AoMs and AoAs (ΔA) plans were also evaluated. Finally, the correlation between geometric similarity and ΔM and ΔA, respectively, was explored.
Results: PTVs coverage and homogeneity differences were not statistically significant ($p < 0.01$) for both Mo- and Ao-based plans. Ao plans OARs sparing was effective for V5 and ipsi-lateral lung Dmean (25% vs 33%, and 5.5 Gy vs 6.6 Gy) as well as for CLB Dmax (5 Gy vs 7 Gy). Mean ΔA was smaller than ΔM for all OARs and it was statistically significant ($p < 0.05$) for the heart Dmax (1cGy vs 16cGy) as well as for the CLB Dmean (2cGy vs 12cGy). Moderate Spearman's-based correlation (>0.4) was found for V10 (vs Max Hausdorff) and V40 (vs Dice and Surface Dice) ipsi-lateral lung as well as for Dmax CLB (vs Dice and Surface Dice) for both Mo- and Ao-based plans. In general, Ao plans returned smaller correlations.
Conclusion: Automated plans resulted generally better than manual plans in OARs sparing, providing dose distributions more robust with respect to OARs delineation differences. Moderate correlations were observed between similarity metrics and OARs dose differences for both manual and automated plan approach with the latter less sensitive to OARs delineation.

Spatiotemporal fractionation schemes using fraction-specific non-coplanar dynamic trajectories

Type: Physics

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Aims: Spatiotemporal fractionation (STF) schemes aim at partial hypofractionation in the tumor along with near-uniform fractionation in normal tissues. This is achieved by delivering different dose distributions in distinct fractions, which are designed such that each fraction delivers a high dose to complementary parts of the tumor while creating a similar dose bath in surrounding normal tissues. In this context, to use the same beam configuration in each fraction seems to be an unnecessary constraint.

We thereby aim to extend STF schemes by using different non-coplanar dynamic trajectories (DTs) in different fractions.

Methods: We developed a column generation-based direct aperture optimization algorithm that simultaneously optimizes different dose distributions to be delivered in distinct fractions, based on their cumulative biologically effective dose (BEDα/β).

Each dose distribution is obtained using an automatically determined, fraction-specific non-coplanar DT consisting of a 360° VMAT arc combined with dynamic couch rotation. A 3-fraction STF plan is generated for a patient with 4 liver metastases using the proposed approach, where a single fraction-specific non-coplanar DT is used in each fraction. This plan (STF1xDT) is benchmarked against a uniformly fractionated (UF) plan that uses 2 coplanar VMAT arcs per fraction (UF2xArcs), a UF plan that uses twice the same patient-specific non-coplanar DT per fraction (UF2xDTs) and a STF plan that uses 2 coplanar VMAT arcs per fraction (STF2xArcs).

Results: For the same tumor BED10 in all plans (equivalent to a physical dose of 3 × 12 Gy), the UF2xArcs plan achieves a mean liver BED4 of 39.6 Gy, while this is reduced to 32.1 Gy (–19%) for the UF2xDTs plan and to 31.0 Gy (–22%) for the STF2xArcs plan. The STF1xDT plan further reduces the mean liver BED4 to 28.6 Gy (–28%), while also shortening the delivery time, as it uses a single 360° DT per fraction compared to two 360° arcs/DTs used in the other plans.

Conclusion: STF plans outperform UF plans in terms of mean liver BED4 reduction. Both the dosimetric benefit and the delivery efficiency of STF schemes can be enhanced by using fraction-specific non-coplanar DTs.

Accuracy and reliability of deep learning-based overall survival prediction in oropharyngeal cancer

Type: Physics

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Aims: The global burden of oropharyngeal cancer (OPC) has increased over the last decades, reaching almost 100,000 new patients in 2020. Radiotherapy with or without concomitant chemotherapy is the gold-standard treatment for OPC, leading to diverse patient outcomes depending on several factors, such as T- and N-category, infection with human papillomavirus, and history of tobacco consumption. In this study, we assessed the accuracy of a deep learning (DL)-based computed tomography (CT) analysis tool for patient overall survival (OS) prediction in OPC. The ability of the model to perform unsupervised, heatmap-based localization of the planning target volume (PTV) was also studied as a measure of the reliability of its predictions.

Our dataset consisted of one internal and two public cohorts of OPC patients ($n=766$) and was split based on OS status after 48 months into training (60%), validation (20%), and test (20%) sets. All CT scans were resampled to a resolution of 2 mm^3 and a sub-volume of 96 × 96 × 96pixels was automatically cropped, which spanned from the nasal columella to the start of the lungs. Models Genesis, a 3D model pretrained on lung CT, was fine-tuned to perform the classification task. Grad-CAM was applied to those test subjects belonging to the internal cohort ($n=22$). The overlap coefficients (OCs) and the Dice similarity coefficient (DSCs) between the resulting heatmaps and the PTVs, defined by an experienced radiation oncologist, were evaluated to assess the reliability of the model.

Regarding OS, the model achieved train/validation/test AUCs of 0.84/0.82/0.81, accuracies of 0.75/0.70/0.71 and F1-scores of 0.72/0.67/0.66. Mean ± std OCs and DSCs of 65.9 ± 8.2 and 37.9 ± 11.0 were observed between the heatmaps and the PTVs of the correctly predicted internal test samples ($n=13$). Mean ± std OCs and DSCs of 59.7 ± 15.5 and 27.0 ± 10.3 were observed between the heatmaps and the PTVs of the incorrectly predicted internal test samples ($n=9$).

The proposed DL model achieved promising predictive performance and reliability. These findings show that DL holds the potential as a non-invasive prognostic tool and bring closer its application in a clinical setting.

Dose guidance in daily adaptive proton therapy: Predicting the cumulative treatment dose

Type: Physics

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Aims: The prescribed treatment dose approved by the radio-oncologist and routinely calculated on the planning CT is assumed to be the dose applied for the whole treatment (ApprovedTD). In online daily adaptive proton therapy (DAPT) however, the plan is optimized online on the daily CT to correct for anatomical daily changes. As such, not only the daily delivered dose, but also the total delivered treatment dose (DeliveredTD) can be more accurately estimated via dose accumulation. Before the end of the treatment series however, and in order to facilitate fraction-specific adjustments and day-to-day decisions, it can be advantageous to predict the DeliveredTD at the end of therapy dose as the treatment is progressing. In this study, two approaches for predicting the total delivered treatment dose (PredictedTD) as part of a DAPT workflow were analysed.

Methods: For both models and for each fraction, each daily adapted plan is accumulated on the planning CT for the already delivered fractions. Dose from propective fractions are then filled in in two ways. With either the initial reference plan optimised on the planning CT multiplied by the remaining fractions, or with the last daily delivered plan multiplied by the remaining fractions. The resulting PredictedTP is calculated for every fraction and compared with both the DeliveredTD and the ApprovedTP. All the calculations are performed for 2 cases with 18 daily CTs each in our house-developed treatment planning system.

Results: For both cases, differences between the PredictedTP and the DeliveredTP are smaller than 0.5GyRBE for more than 87% and of 93% of organ-at-risk and target voxels respectively.

Conclusion: Preliminary results indicate that with both models it is possible to accurately predict the delivered treatment dose. This opens

up the possibility with DAPT to make informed daily decisions based on the delivered cumulative treatment dose.

Evaluating the effect of magnetic field on superficial dose in MR-guided radiotherapy of early laryngeal cancer

Type: Physics

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Aims: PTVs in the head and neck region may require superficial coverage, which can be limited by the build-up effect. Bolus may be used to increase coverage, but they are associated with increased skin toxicity and are labor-intensive. In this study, we investigated whether MR-guided radiotherapy (MRgRT) can provide sufficient superficial dose coverage to the PTV without bolus, due to the electron return effect.
Methods: Fourteen VMAT plans of early laryngeal cancer-patients with superficial PTVs optimized for a conventional linear accelerator (TPS Eclipse, Varian) were compared to IMRT MRgRT plans (TPS MRIdian, ViewRay). VMAT plans were prepared without a bolus (V0) and reoptimized with a 5 mm bolus (VB) and IMRT plans were prepared with correction for the 0.35T magnetic field (IB) and recalculated without correction (I0).

Additionally, film irradiations were performed to validate TPS results. 2D dose measurements were performed in the coronal and transverse plane. For the former, films were taped on the surface of a Delta4 phantom. For the latter, films were placed in between slices of the anthropomorphic Alderson phantom in the neck region. In both cases, films were irradiated with one fraction of the plans described above.
Results: To ease the analysis, all the plans were rescaled to 33×2 Gy. The TPS analysis showed an increased superficial dose to the PTVs in presence of the magnetic field. The mean dose to the most superficial 3 mm of the PTV was 56.5 ± 3.4 Gy for V0, 65.3 ± 0.8 Gy for VB, 65.9 ± 1.2 Gy for IB and 61.9 ± 2.1 Gy for I0.

For the plan reoptimized on the Delta4 the surface dose was 30% lower for V0 with respect to VB and IB, which were in agreement within 8%. Finally, the depth dose curves measurement in the Alderson phantom showed an agreement within 5% with the TPS calculation for the superficial dose and 2% for deeper dose, which is significantly smaller than the relative difference between the values previously reported for IB and V0.
Conclusion: IMRT plans with magnetic field provide a similar superficial coverage in the first 3 mm of the PTV as VMAT plans when a bolus is added. The TPS calculation were confirmed with films measurements.

Synthetic CT for MR-only radiotherapy in the abdomen

Type: Physics

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Aims: Magnetic resonance guided radiotherapy (MRgRT) requires the electron density for computing the dose. This can be accomplished by a synthetic CT (sCT) derived from the MR image. While commercial solutions for sCT have recently become available for head and neck, prostate and brain; further developments are still required for abdomen. We propose a deep learning approach to generate abdominal sCT from 0.35T TrueFISP MR images acquired at a hybrid MRgRT linac.
Methods: This study retrospectively analyzed 93 MR-CT pairs of 76 patients treated in our center. We trained a Cycle-Consistent Generative Adversarial Network (CycleGAN). Compared to other networks, CycleGAN can be trained on weakly paired images. This feature is beneficial for the abdomen area, which is characterized by mobile air pockets affecting the dose. The sCT was analyzed using image and dosimetric parameters. A Student t-test was performed to assess whether DVH parameter differences were statistically significant ($p < 0.05$) and the dose distributions were compared with a 3D gamma analysis (2%/2 mm).
Results: CycleGAN improves the state-of-the-art of models, which in contrast require perfectly aligned image pairs. The image parameters outperformed previously reported results (Mean Absolute Error = 73.1). The generation of bone and air pocket in the sCT was robust, eliminating the need for manual corrections. No differences above 2% were observed in DVH parameters. There was no statistically significant difference between DVH parameters based on CT or sCT. The average pass rates in the gamma analysis were higher than 99%.
Conclusions: The study demonstrates that the generation of sCT using CycleGAN from low field MR images in the abdomen is feasible and allows reliable dose calculation. The image quality parameters outperformed previously reported results and dosimetric parameters were within the clinically acceptable range.

We attribute these improvements to: (i) the training on weakly paired images, (ii) the pre-processing based on a statistical normalization technique and (iii) the greater number of MR-CT pairs analyzed with respect to previous studies.

A non-isocentric dynamic trajectory radiotherapy technique for bilateral whole breast irradiation

Type: Physics

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Aims: Non-isocentric dynamic trajectory radiotherapy (DTRT) extends volumetric modulated arc therapy (VMAT) by dynamic table

movement during beam on. In this study, the use of non-isocentric DTRT for concave targets is explored in a bilateral whole breast irradiation (WBI) case.
Methods: For a bilateral WBI case with a prescribed median dose of 50 Gy to the PTV in 25 fractions, a non-isocentric DTRT technique is developed which allows for more tangential beam directions compared to VMAT. For this, four gantry-table-paths consisting of half gantry arcs with dynamic vertical and lateral table translations are created keeping the central beam axis tangential to the body contour. Two paths range from gantry –180 to 0° and two paths range from 180° to 0°. Then, the intensity modulation along the paths is determined using an in-house Monte Carlo based optimization algorithm, which is able to handle dynamic table translations. The resulting non-isocentric DTRT plan is compared to a VMAT plan consisting of 12 partial arcs in two isocenters. To validate the dosimetric accuracy, the non-isocentric DTRT plan is delivered on a TrueBeam in developer mode and the dose distribution is measured using radiochromic film.
Results: While the dose coverage and homogeneity in the target is similar, the mean heart dose is 6.6 Gy in the VMAT plan and 3.9 Gy in the non-isocentric DTRT plan. In addition, the V5 Gy and V20 Gy of total lung volume are 90% and 13% in the VMAT plan and 29% and 7% in the non-isocentric DTRT plan. The Dmax to the spinal canal is 4.6 Gy in the VMAT plan and 1.4 Gy in the non-isocentric DTRT plan. The passing rate of the gamma analysis comparing measured and calculated dose distributions is 99% using a 3% (global)/2 mm criterion with a 10% dose threshold.
Conclusion: The non-isocentric DTRT plan for a bilateral WBI resulted in substantially reduced dose to the heart and lung while maintaining the target homogeneity in comparison to the VMAT plan. Furthermore, the dosimetric accuracy of the non-isocentric DTRT was validated successfully.
Acknowledgments: This work was supported by the Swiss National Science Foundation and by Varian Medical Systems

Splitted VMAT technique versus conventional VMAT applied to left breast cancer treatment

Type: Physics

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Aim: VMAT technique is increasingly used for breast cancer radiotherapy treatment in order to obtain conformal dose distribution at the cost of higher low dose volume. A pronounced axilla region, close OARs and particular anatomy could lead to VMAT choice. The purpose of this work is to propose a new VMAT technique in order to reduce OARs doses.
Methods: Twenty left breast cancer volumes were planned with two different VMAT techniques: a new splitted VMAT (S-VMAT) technique and the conventional breast VMAT used in our center (C-VMAT). C-VMAT consists of two partial arcs (300 to 179° collimator 5–30° and 179 to 300° collimator 330–355°) while S-VMAT consists of 2 splitted arcs (300 to 60° collimator 5°, 60 to 179° collimator 355°, 179 to 60° collimator 5°, 60 to 300° collimator 355°). The advantage to use this conformation is to change the collimator angle for every single splitted arc in order to adapt it to the PTV shape, shielding OARs and contralateral region. All plans were calculated in the Eclipse Treatment Planning System using Acuros 16.1 algorithm. Plan quality and efficiency were assessed evaluating PTV coverage and OARs sparing for all plans.
Results: A Wilcoxon signed rank test was used to evaluate differences between S-VMAT and C-VMAT. There were no statistically significant differences in homogeneity, conformity, V95% and V105% but S-VMAT showed superiority compared to C-VMAT in order to reduce monitor units ($P<0.05$). For heart, contralateral lung and contralateral breast, S-VMAT significantly reduced V5 Gy and mean dose compared with C-VMAT ($P<0.05$). Moreover, V20 Gy and mean dose were analysed for ipsilateral lung, Dmax was evaluated for LAD and the differences between techniques turned out to be statistically significant ($P<0.05$).
Conclusion: S-VMAT maintains similar PTV coverage and reduces monitor units compared to the C-VMAT. At the same time the splitted arc technique allows a better sparing of all OARs.

Pilot studies using an ESHO quality assurance phantom for phased-array deep hyperthermia devices

Type: Physics

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Aims: Phantoms for quality assurance (QA) of deep hyperthermia therapy (DHT) devices are not commercially available. In this work, we suggest an easy to build phantom to perform commissioning and regular QA on the performance of DHT phased-array devices.
Methods: The phantom container consists of a 64 cm long polyurethane tube with an external diameter of 25 cm and a wall thickness of 8 mm, where both ends are sealed with discs. Inside the tube, 3D-printed structures hold 13 catheters spaced by 3 cm and distributed in a cross shape. The catheters are the same as those used for DHT treatments (6F, 35 cm, Med-Implant, Keltern, Germany). The central catheter is extended to cover the full length of the container. The phantom is filled with a tissue-equivalent gel. After placing the phantom in the BSD-2000 3D Sigma Eye applicator (Pyrexar Medical, Salt Lake City, USA), a power pulse of 1000 W for 10 min at 100 MHz is applied, with equal amplitudes and phase settings to target the center of the phantom. Temperature is recorded inside the catheters using thermistors provided with the BSD-2000 3D system. A scanning method with a 5 mm step is performed for the longitudinal axis measurement. From the longitudinal data, the position of the center and the extension (full width at half maximum, FWHM) of the heated volume is determined.
Results: A maximum temperature rise of $\Delta T = 7.6$ °C was measured at the center of the phantom after the 10 min power pulse. Along the longitudinal axis, a high-resolution profile is achieved over a length of 60 cm. From the longitudinal data the position of the center and the extension (full width at half maximum–FWHM = 32.5 cm) of the heated volume can be determined. In the vertical and horizontal directions, only the position of the center is clearly defined by fitting a polynomial curve.
Conclusions: The proposed phantom allows the commissioning of new devices and regular QA measurements for DHT phased-array systems. Fast temperature rise measurements can be used to determine the FWHM in the longitudinal direction and the center of the heating focus in all three spatial directions.

A novel approach for combined proton-photon therapy of multi-metastatic cancer patients

Type: Physics

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Aims: Combined proton-photon therapy (CPPT), where most fractions are delivered with photons and only a few are delivered with protons, may represent a practical approach to optimally use limited proton resources. Previous studies showed that CPPT performs better when an overproportionate dose is delivered to the tumor with the proton fractions. In this work, we extend such an approach by determining the optimal proton and photon dose contributions to individual lesions for patients with multiple metastases.
Methods: CPPT plans are generated by simultaneously optimizing distinct IMPT and IMRT dose distributions based on their cumulative biologically effective dose (BEDα/β). The dose contributions of the proton and photon fractions to each individual metastasis are handled as additional optimization variables in the fluence map optimization problem using a new planning objective, which also ensures that similar spatial dose distributions are delivered within each lesion in all fractions. Five- fraction and three-fraction CPPT plans, in which one fraction is delivered with protons and the remaining fractions with photons, are generated for a patient with 4 liver metastases (patient A) and a patient with 30 brain metastases (patient B), respectively, and benchmarked against uniformly fractionated IMRT and IMPT plans.
Results: For patient A, the IMRT plan achieves a mean liver BED4 of 29.9 Gy, while this is reduced to 17.0 Gy (–43%) with the CPPT plan and to 16.3 Gy (–45%) with the IMPT plan. Similar results are obtained for patient B, for which the mean brain BED2 is reduced compared to the IMRT plan (12.3 Gy) by 27% with the CPPT plan and by 21% with the IMPT plan. The dose contribution of the single proton fraction to the individual metastases varies from 67 to 93% of the tumor BED10 for patient A and from 24 to 84% of the tumor BED10 for patient B.
Conclusion: CPPT outperforms IMRT in terms of BED reduction to critical organs and approaches (or even improves) the IMPT plan quality, while using only a single proton fraction. The proposed approach allows to deliver different proton dose contributions to distinct metastases, depending on their size and location.

Tumour control probability for hypoxia-guided proton therapy in non-small cell lung cancer and the role of reoxygenation

Type: Physics

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Aim: Tumour hypoxia is associated with radioresistance and is an important limiting factor for tumour control. We evaluated the impact of inter-fraction reoxygenation on outcomes following conventional and dose escalated proton therapy of non-small cell lung cancer (NSCLC).
Methods: A mechanistic tumour control probability (TCP) model accounting for the additional effects of tumour repopulation and reoxygenation [1] was cross-calibrated to clinical data of lung radiotherapy (2–4 Gy/fx [2]). Based on this model, TCPs were calculated for competing treatment approaches in 10 NSCLC patients, comparing homogeneous dose distributions with treatments including dose escalation of the hypoxic region within the GTV. Dose escalation plans were generated based on Hypoxia-PET imaging and oxygen enhancement ratio (OER) modelling for protons [3].
Results: The model predicts an increase in TCP of up to 21% for hypoxia-guided dose escalation treatment plans, depending on the degree of hypoxia in the individual patients. The average increase in TCP achieved by dose escalation was 14%, 3%, and 1% for simulated inter-fraction reoxygenation rates of 2.5%, 10%, and 40%, respectively.
Conclusions: Hypoxia-guided dose escalation in proton therapy can mitigate losses in local control, with a larger benefit at low reoxygenation rates.

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Utilizing robust optimized mixed beam radiotherapy to avoid using a bolus

Type: Physics

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Aims: The use of a bolus in photon beam radiotherapy for targets close to the body surface is associated to placement uncertainties affecting the dose distribution or even the risk to accidentally omit the bolus. The aim of this work is to evaluate whether robust optimized plans for mixed photon and electron beam radiotherapy (MBRT) can maintain treatment plan quality without using a bolus.
Methods: MBRT plans consist of photon multileaf collimator (MLC) shaped photon and electron apertures to be delivered on a TrueBeam. For this study, cylindrical phantoms are designed with a clinical target volume (CTV), a serial and a parallel organ at risk (OAR). Each phantom varies in the depth of the CTV measured from the body surface.

Beamlet dose distributions were calculated using Monte Carlo simulations for five 6 MV photon fields at five gantry angles and six electron fields from one gantry angle with beam energies of 6, 9, 12, 15, 18 and 22 MeV. Using these beamlets, robust optimized MBRT plans

consisting of 50 apertures are created for CTV depths = 0.0, 0.2, 0.4, 0.6, 0.8 and 1.0 cm, with and without a 0.5 cm bolus. The same optimization objectives were used for all plans and the robust optimization considered the nominal scenario and six error scenarios (±0.5 cm translational systematic setup error in three main axes). The plans were compared in terms of objective function values and dose volume histograms (DVHs).

Results: The treatment plans without bolus performed 13% better for 0.8 and 1.0 cm CTV depth, comparable for 0.4 and 0.6 cm, and 27% worse for 0.2 and 0.0 cm, when comparing the objective function values to those of the plans with bolus. However, the differences in the DVHs were minor between the plans created with or without bolus for each investigated CTV depth.

Conclusion: Similar treatment plan quality was observed for robust optimized MBRT plans with or without bolus, suggesting that it is not necessary to use a bolus. However, the findings need to be confirmed with clinical cases.

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Estimation of immunosuppressive effects of proton therapy on circulating lymphocytes

Type: Physics

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Protontherapy

Aims: During radiotherapy, a significant fraction of the highly radiosensitive lymphocytes that are part of the immune system can be damaged as a result of the absorbed dose. Treatment-related lymphopenia is a common side effect after radiotherapy that can last several years and has been associated with reduced survival for various cancer types. This work focuses on the estimation of the dose delivered to circulating lymphocytes as they pass through irradiated organs.

Methods and Materials: The simulation of the dose delivered to the blood and thus to the circulating lymphocytes used in this work is based on the computational framework HEDOS. This framework simulates the blood flow between all major organs of the human body, which is then combined with organ dose-volume histograms to calculate the dose delivered to each blood particle during a treatment. In order to consider the dynamic beam delivery of pencil beam scanning proton therapy, a novel dose calculation algorithm was devised that explicitly simulates the dose delivered with each pencil beam. This new method was used to analyse, for a liver irradiation, the effect of various treatment planning parameters on the blood dose-volume histogram, especially on the fraction of blood receiving at least 0.5 Gy which can be viewed as threshold dose to inactivate lymphocytes.

Results: While no significant difference was found between pencil beam scanning and passive scattering, the beam delivery time had a strong impact on the dose delivered to the blood. The volume of blood receiving at least 0.5 Gy decreases from 81% for a 36s delivery time to 63% for a 9 s delivery time. Hence, developments in pencil beam scanning to reduce beam delivery times, such as the use of higher dose rates and the optimization of the scanning process have the potential to reduce the severity of radiation induced lymphopenia.

Fully automated intensity-modulated proton therapy planning for head-and-neck patients using machine learning and meta-optimisation

Type: Physics

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Aims: Intensity-modulated proton therapy (IMPT) bears the potential to create highly conformal dose distributions. This technique has proven its ability to spare organs at risk (OARs) while depositing the desired dose in the tumour, but the treatment planning is a time consuming and largely empirical process. We present a novel fully automated IMPT planning algorithm for head and neck cancer patients for our in-house treatment planning system at the Centre for Proton Therapy.

Methods: Two novel contributions are presented. First, a novel machine learning model selects the beam arrangement based on a training set of 87 patients treated at the Centre for Proton Therapy. Such a model requires less than a minute for the beam arrangement selection. Second, the beam arrangement is combined with a novel heuristic meta-optimisation algorithm to tune the objectives for our existing spot optimiser. The objectives are then used to optimise the spot weights and obtain the final dose distribution. The only input to the algorithm are the CT, structure contours and prescriptions. We apply the automation method to a test set of 19 head-and-neck patients and compare the obtained plans retrospectively to the clinically accepted plans.

Results: The overall performance of the automatically generated plans in terms of target coverage and mean and maximum dose to OARs is comparable to the manually created plans. The median difference between the manually defined and automatically generated plan is close to zero. The mean and standard deviation of the planning time for the automation solution are 21 ± 17 min, the maximum planning time is 55 min.

Conclusion: The automatic planning tool comes close to the performance of human planners at moderate computational costs. Manual fine tuning is possible, but not yet investigated. The associated time savings will be beneficial for our clinic, even though not all plans might be clinically acceptable without manual fine-tuning. They can nevertheless still serve as a starting point and baseline plan for the human planners and potentially reduce the planning time.

Monte Carlo dose computation to replace measurements for Patient Specific Quality Assurance

Type: Physics

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Aim: To implement fast Monte Carlo (MC) dose computation engine FRED in water within the PSI proprietary TPS FIonA in order to streamline Patient Specific QA (PSQA).

A role of PSQA is to verify the accuracy of the clinical dose computation engine. This is presently achieved by delivering every single

clinical field to a water phantom and measuring dose at a given depth with a 2D IC array. The aim of the project is to replace this time-consuming step by using the independent GPU-based MC dose computation engine FRED1, and to predict field specific dose correction factors necessary due to known limitations of the fast analytical calculation used in FIonA.
Method: FRED has been parametrized to the PSI Gantry 2 beam model and integrated into our FIonA TPS as an independent dose computation engine. Commissioning of FRED in water was performed by comparing FRED calculations against measurements of basic beam characterization, i.e. Integral Depth Dose (IDD) curves, spot profiles as well as absolute dose and profiles of 74 Spread-Out Bragg Peak (SOBP) of various field sizes, depths and modulations. Its performance was subsequently assessed against actual PSQA of clinical fields, measured in water with a PTW 2D-array.
Results: FRED shows a very good agreement with absolute dose and profile measurements of both IDDs and SOBPs. IDD ranges agree within 1 mm, and absolute point dose measurements within SOBPs agree within 0.98 ± 1.12% (SD), whereas the analytical algorithm accuracy is 3.01 ± 3.24% (SD). The analysis of the clinical fields is still undergoing at the time of writing.
Conclusion: Implementation of MC dose computation engine FRED into PSI TPS FIonA allows direct dose comparison in water between the clinically used analytical algorithm and a fully independent MC computation engine. After commissioning, FRED is planned to replace measurements to verify the accuracy of the clinical dose distribution in water, without affecting the PSQA quality. On the contrary, it would considerably save time (up to 6 h/week), with the additional advantage of offering 3D dose validation, unlike the current measurements performed at PSI.

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Deformable dose accumulation uncertainties for combined proton-photon therapy

Type: Physics

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Aims: Optimally combined proton-photon therapy (CPPT) could increase the cost-effectiveness of proton therapy for non-small cell lung cancer (NSCLC) compared to IMRT [Amstutz 2022]. However, for indications undergoing anatomical changes, such as NSCLC, adaptive strategies are necessary. One component of adaptive strategies is deformable dose accumulation (DDA). Recent work showed considerable DDA uncertainties for IMPT [Nenoff 2020]. Therefore, this work investigates DDA uncertainties for CPPT.
Methods: Five NSCLC patients were investigated, each with a planning CT (planCT) and three repeated CTs (repCTs). First, repCTs were rigidly registered to the planCT, followed by deformable image registration (DIR) with five different algorithms. For each patient CPPT, IMPT and IMRT treatment plans were optimized. The DDA uncertainty was assessed by a previously proposed method [Nenoff 2020], for which the fraction dose is individually warped with each of the five DIR algorithms to the planCT. The uncertainty is calculated as the voxel-wise max-min across the warped fraction doses. The evaluation of the uncertainty was performed on a structure level. The reported results are the average over the repCTs and the five patients. In the following, we report the DDA uncertainty in percentage of the prescribed dose for which 98% of the non-zero uncertainty voxels were below (DDAU98%).
Results: In accordance with the earlier publications about IMPT, the largest DDA uncertainties are located in the dose gradient regions for all plans (CPPT/IMPT/IMRT). In the PTV the DDA uncertainties were very similar for all treatment modalities, as large parts have relatively homogenous doses. For heart/esophagus partly within the dose gradient region, DDA uncertainties were larger for IMPT compared to CPPT and IMRT.

On the other hand, the regions with non-zero DDA uncertainties are smaller for IMPT, due to the smaller amount of irradiated tissue.

DDAU98%[%]/CPPT/IMPT/IMRT
PTV/11.5/12.6/11.2
Heart/7.4/12.2/7.8
Esophagus/17.8/24.2/14.8

Conclusion: DDA uncertainty for CPPT is reduced compared to IMPT at the cost however of distributing uncertainties over a larger region.

Repair protein damage vs. cell repair saturation: A comparison of its use in radiobiological models

Type: Physics

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Aims: Most of the actual radiobiological models consider only DNA as target of study. But other cellular elements may also have a capital role for survival, e.g. the availability and/or efficiency of repair proteins. Consequently, they should be covered by models as well. There are different hypotheses about how repair proteins can be affected by radiation, but none of them is sufficiently corroborated by experimental studies. This work compares the ability to explain diverse radiobiological effects of two hypothetical mechanisms: protein radiation-induced damage and cell repair saturation.
Methods: We used the Multi-Hit Repair (MHR) model. In its original formulation, it already included a radiation-induced protein damage mechanism. With protein damage, the MHR-model exhibits a proven capability to cover experimental data from different biological tests such as clonogenic–and comet assay. We compared these results with those from a formulation in which protein damage is substituted by saturation of repair proteins. In order to obtain a repair-saturated mechanism, Michaelis-Menten kinetics were introduced in the repair function of the MHR model.
Results: Both protein-related models were able to explain radiobiological effects as linear-quadratic-linear (LQL) survival curves or dose-rate survival effects like exponential survival curves at low dose rates (~0.01 Gy/min) or the increase of the survival with the reduction of the dose-rate in the range of 0.1–2 Gy/min.
Conclusion: Due to the previously mentioned lack of experimental data in this field, it is impossible to decide which of these two protein mechanisms is closer to reality. However, the repair saturation mecha-

nism simplifies the MHR model because it works with one parameter less than in its original formulation, which could be essential because of the problems encountered in the past to obtain a proper model calibration.

The ability of the proposed repair saturation mechanism to cover essential aspects such as dose-rate dependence and LQL-behaviour of survival indicates that it constitutes an alternative explanation to the repair protein damage mechanism for radiation used in the original MHR model.

A cell kill based treatment planning approach for polymetastatic cancer patients incorporating motion uncertainties

Type: Physics

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Aims: Early and maximum local consolidative radiotherapy of all metastases that do not achieve complete response to systemic therapy is a novel treatment strategy to improve outcomes of polymetastatic cancer patients. Traditional planning approaches, in which each lesion is treated to the same dose, are not suitable in terms of efficacy for targeting multiple metastases across the body. As local ablation of all visible metastases may not be possible due to OAR dose constraints, it is in fact unclear what dose can or should be prescribed to each lesion. To address this problem, we implemented a radiotherapy planning approach that maximizes tumor cell kill and simultaneously preserves organ function, where motion uncertainties are incorporated using a coverage probability approach.
Methods: A linear-quadratic cell survival model is assumed according to which the number of surviving tumor cells is

$\Sigma i \in PTV Ci \exp(-(\alpha di+\beta di2)N)$

where di is the dose per fraction in voxel i and N is the number of fractions. To handle motion uncertainties, a coverage probability approach is proposed, where $Ci=\Sigma j \in GTV cjpij$ is the expected cell density in voxel i obtained from convolving a uniform cell density c in the GTV with a Gaussian kernel p ($\sigma=3$ mm). Five-fraction SBRT plans that minimize the number of surviving tumor cells were generated for 3 melanoma patients with multiple lung and liver metastases, subject to OAR constraints.
Results: The cell kill based planning approach delivers different doses to different metastases, with the mean dose varying between the lesions by up to 10 Gy. Our approach exploits the fact that, for given OAR dose limits, lesions at favorable anatomical locations can be irradiated to higher doses than others. When handling motion uncertainties by nonuniform coverage probabilities, a larger dose is delivered to the GTV voxels, while slightly compromising the dose in the GTV-to-PTV margin expansion.
Conclusion: The proposed cell kill based treatment planning approach allows for personalized treatments of polymetastatic cancer patients, thereby overcoming the limitations of traditional planning approaches of delivering the same homogeneous radiotherapy dose to each lesion.

Combined proton-photon radiotherapy for prostate cancer using a horizontal fixed proton beamline

Type: Physics

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Aims: Proton therapy is a limited resource, mainly due to the high cost and bulkiness of the proton gantry. Integrating a horizontal fixed proton beamline (FBL) into a conventional treatment room with a Linac and a robotic couch, allowing protons and photons to be delivered in the same fraction, might increase the availability of proton therapy. This concept is studied for prostate cancer including nodal irradiation.
Methods: The optimal combined proton-photon treatment (CPPT) is determined through simultaneous optimization of the cumulative physical dose using a hybrid robust planning approach (a PTV margin for setup/motion and a probabilistic approach for range uncertainties of +/– 3.5%). Photons are delivered with a full VMAT arc, and for IMPT 4 beams in the coronal plane are used. The considered patient lies in supine position. Planning objectives are to deliver 57.75 Gy to the prostate and 45 Gy to the nodal target, achieve conformity, and minimize the mean dose to the bladder, rectum and remaining healthy tissue (HT).
Results: Compared to VMAT-only treatments, CPPT reduces the mean dose: from 24.6 to 21.8 Gy (bladder), from 25.1 to 22.6 Gy (rectum), and from 6.5 Gy to 4.7 Gy (HT). In CPPT, on average, protons (mean dose of 24.4 Gy) and photons (mean dose of 23.6 Gy) contribute approximately the same amount of dose to the whole target. Photons are mainly delivered through anterior and posterior beams, which are not deliverable with an FBL in lying position.

In particular, photon beams are used to improve the conformity and robustness of the dose distribution at the interface of prostate and rectum, and thereby improve treatment plan quality compared to IMPT-only treatments. Indeed, for IMPT-only, the mean rectum dose is 27.8 Gy, and the target is underdosed in the case of an undershoot of proton beams.
Conclusion: CPPT with an FBL may make proton therapy available to a larger patient population including prostate cancer patients. It may reduce normal tissue dose compared to VMAT-only, and may improve conformity and robustness compared to IMPT-only.

NTCP-based plan comparison between two proton planning approaches for head and neck cancers

Type: Physics

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Aims: A normal tissue complication probability model (NTCP)-based method to select head and neck cancer (HNC) patients for photon or proton therapy has been approved by the Dutch Health Care Institute and is part of the clinical routine in the Netherlands [1]. In this study, we used this NTCP model for comparing two different proton planning approaches.
Methods: Six HNC patients with different HNC diagnosis, have been planned with Eclipse (version 16.01.10, Varian Medical System, Palo Alto, CA) at PSI using two different beam arrangements (BAs). Specifically, a 6-beam non-coplanar BA, used at PSI, and a 4-beam coplanar BA, described in [1]. Both BAs were planned using multi field optimization and split-target concept techniques, in addition to robust optimization. The target coverage was kept comparable meanwhile the relevant organs at risk (OAR) were spared to the best of the specific technique's capacity. In addition to OARs already included in the NTCP model, i. e. pharyngeal constrictor muscles (PMC) superior/medium/inferior, parotids, oral cavity and submandibular glands, other relevant OARs were evaluated, i. e. brainstem and larynx.
Results: Plans based on 4-beam coplanar BA technique resulted in a generally lower mean dose to the medium and inferior PCMs (on average, 46.8 GyRBE vs 50.8 GyRBE and 26.7 GyRBE vs 33.6 GyRBE respectively). This led to better NTCP outcomes, potentially improving patients' quality of life. On the other hand, brainstem and larynx received in general higher mean dose (on average, 44.5 GyRBE vs 29.2 GyRBE and 36.8 GyRBE vs 23.7 GyRBE respectively), which might lead to increased radiation-induced toxicity for these organs.
Conclusion: This study shows that different beam setups, together with diverse target splitting, can lead to large differences in dose distribution, especially in relation to the sparing of specific organs at risk and may be thus associated with different NTCPs. A hybrid technique may be the aim of further investigations.

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Development of dynamic-collimator trajectory radiotherapy (colli-DTRT)

Type: Physics

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Aims: colli-DTRT extends state-of-the-art VMAT by non-coplanar arcs and dynamic-collimator rotation. Table-angle, gantry-angle range, and dynamic-collimator paths are optimized based on contoured structures. In this work, colli-DTRT is compared to coplanar-VMAT to investigate its potential for organ-at-risk (OAR) sparing.
Methods: A gantry-table cost-map is calculated using fractional target/OAR volume-overlap in beam's-eye-view for all beam directions. The map is thresholded and candidate paths (partial arcs) are defined. Candidates spanning >30° gantry-angle range are ranked based on cost (lowest preferred) and gantry-angle range (largest preferred). The final set of paths is chosen based on the summed rank to approach a user-defined total gantry-angle range. Dynamic-collimator rotation minimizes field-width in MLC travel-direction. Finally, colli-DTRT paths are imported into a research version of the Eclipse TPS for intensity modulation optimization.

colli-DTRT plans were created for the elective target volume (25 × 2 Gy) of two head- and-neck (HN) cases on an anthropomorphic phantom and dosimetric plan quality was compared to coplanar-VMAT plans. Deliverability and dosimetric accuracy of colli-DTRT was validated by film dosimetry for one case.
Results: Target coverage was similar for both techniques and cases. For HN1 (nasopharyngeal carcinoma), D0.03cc to contralateral (CL) lens and optic nerve (ON) were reduced by 2.0 and 4.9 Gy with colli-DTRT compared to coplanar-VMAT. D0.03cc reduction for ipsilateral lens and ON was 1.8 and 2.2 Gy, respectively. For HN2 (adenoid cystic carcinoma), Dmean to pharynx, oral cavity, CL parotid and CL submandibular gland were reduced by 1.7, 4.3, 2.6, and 0.8 Gy, respectively, for colli-DTRT compared to coplanar-VMAT.

The plan for HN2 was successfully delivered on a TrueBeam in developer mode. Gamma passing rate was >99% (3% (global)/2 mm, 10% threshold) for measured vs. calculated dose.
Conclusions: By optimizing beam angles, colli-DTRT resulted in favorable OAR sparing for two HN cases compared to coplanar-VMAT. Deliverability was successfully validated against film measurements.

This work was supported by Varian Medical Systems.

NTCP robustness to patient-setup uncertainties

Type: Physics

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Aims: To assess the robustness of volumetric modulated arc therapy (VMAT) and dynamic trajectory radiotherapy (DTRT) treatment plans for two treatment sites to systematic and random patient-setup uncertainties with regard to their NTCP score.
Methods: VMAT and DTRT plans are created for three head-and-neck (HN) cases: One postoperative Adenoid-Cystic Carcinoma (ACC) of the left parotid gland, two locoregionally advanced head-and-neck squamous cell carcinomas (HNSCC) with bilateral elective nodal irradiation, (all sequential boost to 50/66/70 Gy in 2 Gy per fraction) and two locally advanced lung cases prescribed to 60 and 66 Gy. The impact of rigid systematic (s) and random (σ) patient-setup uncertainties (translations and rotations) on the dose distribution are calculated using an in-house developed robustness tool (per axis: HN: s ≤ 5 mm/4°, σ = 2 mm; Lung: s ≤ 6 mm/4°, σ = 4 mm).

NTCP of HN cases is evaluated with the model used in dutch indication protocol for proton therapy for HNSCC (LIPPv2.2, xerostomia, dysphagia) and lung cases with a multivariable dyspnea model and the QUANTEC Lyman-Kutcher-Burman model for pneumonitis.
Results: The nominal DTRT plans for the three HN score lower NTCP values compared to the respective VMAT plans for all investigated endpoints (up to –7.1% for xerostomia grade ≥II). The observed deviations in NTCP score are –6 to 8.3% and –7 to 8.8% for the two HNSCC cas-

es and –1.4 to 2.5% for the ACC case. NTCP score deviation for the lung cases is <2% for all endpoints for both DTRT and VMAT. NTCP scores of all plans are less sensitive to rotations than shifts for the investigated uncertainties. Random setup uncertainties impact the NTCP score by <0.3% (HN) and <0.1% (lung) for all endpoints. Depending on the alignment and shape of the dose distribution, plans show different NTCP robustness (e. g. one VMAT plan for HN is less robust in the opposite rotational direction as the respective DTRT plan).
Conclusion: NTCP robustness is successfully assessed for HN and lung cases. Setup uncertainties can have substantial effects on calculated NTCP scores for the investigated cases. This work was partially supported by Varian Medical Systems, Inc.

Deep-inspiration breath-hold reproducibility in cine MV images of IMRT lung treatments

Type: Physics

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Aims: This study used cine MV images to investigate the reproducibility of deep inspiration breath-hold (DIBH) in lung cancer patients treated with intensity-modulated radiotherapy (IMRT). A method for markerless lung tumour localization was developed and used to determine the difference in internal tumour position between setup cone-beam CT (CBCT) imaging and treatment delivery.
Methods: Cine MV images were recorded at 7.5 Hz during all field deliveries for seven lung tumour patients treated with IMRT in DIBH. The tumour motion during each DIBH IMRT field delivery will typically be small. It allowed generation of a composite MV image of the entire field area by stitching together cine MV frames of the IMRT segments. Digitally reconstructed radiographs (DRR) were generated by ray tracing through the setup CBCT. A DRR containing most of the anatomy except the tumour was subtracted from the composite MV image to enhance the tumour contrast. The tumour position was then determined in the contrast-enhanced MV image by template matching using a DRR of the tumour as template. It yielded the tumour position at treatment relative to the intended position in the setup CBCT.

Margins accounting for the tumour motion between setup CBCT and treatment were calculated using the van Herk formalism.
Results: Cine MV images of 568 field deliveries (155 fractions) were analysed. Markerless tumour localization allowed determining the intrafraction tumour shift between setup CBCT and treatment delivery in 76% of the IMRT fields. The setup margins were calculated as described in Table 1, where Σ and σ are the standard deviations of systematic and random setup errors, respectively. Margins were between 3.8 and 5.5 mm in different directions. In addition, a significant systematic drift of 3.5 mm in the cranial and 1.2 mm in the posterior direction was found ($p<0.01$).
Conclusion: A method for lung tumour localisation in cine MV images of DIBH IMRT was developed. It showed a systematic tumour drift in cranial and posterior direction between setup CBCT and treatment.

Table 1

[mm]	CC	LR	AP
Mean	3.5*	0.3	–1.2*
Σ	1.0	1.2	1.6
σ	1.9	1.2	2.1
$2.5\Sigma+0.7\sigma$	3.8	3.9	5.5

*significic antly different from zero ($p<0.01$)

Lower superior-inferior isocenter position in complex hybrid-breast technique for breast cancer patients with lympho-nodal irradiation

Type: Physics

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Aim: To investigate the outcome of a lower set isocenter in complex Hybrid-Breast technique planning for breast cancer irradiation versus published standard VMAT techniques.

Materials and methods:

10 patients with advanced breast cancer (6 right and 4 left-sided) receiving adjuvant radiotherapy including nodal irradiation (supraclavicular and internal mammary chain) were assessed. The lower isocenter Hybrid-Breast technique configures IMRT tangential fields combined with VMAT tangential arcs designed to reduce the dose at normal tissue as well as the low-dose bath area produced by the standard VMAT technique. DVH metrics of planning target volumes (PTV), contra-lateral breast, bilateral lungs and the heart were analyzed and compared to published data.
Results: The coverage of V47.5 Gy of PTV breast was 96.6% vs 96.9% [1], for the nodal PTV was lower the V95% isodose was 92.5% vs 99.4% [1]. The dose at ipsilateral lung showed a large reduction in lower dose levels: the V20 Gy, V10 Gy and V5 Gy were 18%, 29.9% and 48.3% vs 27.3%, 45.7% and 74.6% [2] and 16.9%, 40.3% and 70.2%, respectively [1]. The same was true for the mean heart dose with 2.3 Gy vs the 10.9 Gy [1] and 11.7 Gy [2]. Mean dose to the contra-lateral breast was equivalent with 3.5 Gy vs 3.6 Gy [2] and 2.9 Gy [1].
Conclusion: With this new technique we can achieve a significant reduction in dose to normal tissue, especially less lower doses to lungs and heart. The PTV coverage is equivalent for PTV breast, but lower for the nodal PTV, which can be explained partially by some strict departmental constraints to some organs-at-risk.

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Generation of synthetic multi-breaths 4DCT imaging to model irregular breathing

Type: Physics

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Aims: 4DCT is the clinical standard for imaging organ motion in radiotherapy. Being an average over multiple breathing cycles (BC) during a limited time scale, it is however questionable to what extent these images are representative of the patient's respiratory variability in daily treatment fractions. We introduce a method to combine repeat volumetric 4D images into multi-breath CT datasets such that motion irregularities can be included.
Methods: From a reference and repeat 4DCTs, several steps of deformable image registration are used to extract the respiratory motion and deform the images to represent a sequence of BC.

First, average images (Mid Position, MP) per breath are computed and registered to model the inter-session variations in anatomy and positioning that may occur in images acquired on different days. Afterwards, each MP is registered to the corresponding breathing phases, thus modelling the motion of each breath. Finally, these BC specific vector fields are warped by the inter-session deformation to generate a synthetic multi-breath dataset from the reference 4DCT MP. This technique was tested on a dataset of 6 NSCLC patients with tumours in different lobes. The trajectory of the GTV center of mass was extracted to analyse motion amplitude and baseline drift over five reconstructed BC, and Jacobian maps analysed to quantify the extent of tumour volume change.
Results: Starting from a breathing amplitude in the reference 4DCT of 10 mm for tumours in the lower lobe and 6.9 mm in the upper one, observed amplitude variability after combination of repeated 4D images was as high as 14.4 mm and 10.4 mm (44% and 51% variations with respect to reference) respectively, with baseline drifts of up to 1.9 mm and 3.1 mm. These variations were associated with GTV volume expansions of up to 98% tumour voxels in full inhale, and 83% contraction in exhale phase.
Conclusion: 4DCT data can be extended to model variable tumour respiration and deformation patterns by adding synthetic phases from time-resolved repeated images. Even though our validation was based on repeated CT images, the method can also be applied to multimodal datasets such as 4D magnetic resonance imaging.

Estimation of immunosuppressive effects of proton therapy on circulating lymphocytes

Type: Physics

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Aims: During radiotherapy, a significant fraction of the highly radiosensitive lymphocytes that are part of the immune system can be damaged as a result of the absorbed dose. Treatment-related lymphopenia is a common side effect after radiotherapy that can last several years and has been associated with reduced survival for various cancer types. This work focuses on the estimation of the dose delivered to circulating lymphocytes as they pass through irradiated organs.
Methods: The simulation of the dose delivered to the blood and thus to the circulating lymphocytes used in this work is based on the computational framework HEDOS.

This framework simulates the blood flow between all major organs of the human body, which is then combined with organ dose-volume histograms to calculate the dose delivered to each blood particle during a treatment. In order to consider the dynamic beam delivery of pencil beam scanning proton therapy, a novel dose calculation algorithm was devised that explicitly simulates the dose delivered with each pencil beam. This new method was used to analyse, for a liver irradiation, the effect of various treatment planning parameters on the blood dose-volume histogram, especially on the fraction of blood receiving at least 0.5 Gy which can be viewed as threshold dose to inactivate lymphocytes.
Results: While no significant difference was found between pencil beam scanning and passive scattering, the beam delivery time had a strong impact on the dose delivered to the blood. The volume of blood receiving at least 0.5 Gy decreases from 81% for a 36s delivery time to 63% for a 9 s delivery time.
Conclusion: Developments in pencil beam scanning to reduce beam delivery times, such as the use of higher dose rates and the optimization of the scanning process have the potential to reduce the severity of radiation induced lymphopenia.

Simulation of on-line range verification of proton therapy using the PETITION PET detector

Type: Physics

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Aim: Range verification of proton therapy using imaging of secondary particles generated during treatment, as in PET imaging, requires thorough understanding of both the predicted distribution of positron emitting isotopes within the patient, as well as the scanner response both during and post irradiation.
Methods: We introduce a simulation workflow which combines simulation of the production of positron emitting isotopes in the patient using the GPU accelerated Monte Carlo code Fred, integration of the delivery timing and beam tune, and simulation of the online and post irradiation acquisition of PET data with the open ring PETITION scanner using GATE.

Imaging of short-lived isotopes such as 12N, t1/2 = 11 ms, provides immediate feedback during treatment, however poses significant chal-

lenges due to decay times comparable to spot delivery times, large positron range, low production in non-fatty tissues, and signal from other longer lived isotopes. We simulate production of isotopes for individual spots and energy layers depending on the decay time relative to delivery time.
Results: The workflow is utilized to investigate variations in treatment delivery techniques which boost the on-line signal for prompt feedback as well as impact post irradiation imaging, such as inversing of the energy delivery sequence, increased dose rates, and spot reduced planning. For example, the proportion of coincidences due to 12N decays after delivery of the first energy layer of a spread out Bragg peak in a simple phantom is 77%, however decreases to 16% after delivery of the final energy layer due to ongoing production of longer-lived isotopes such as 10C, 11C, and 15O. By switching the energy delivery sequence and increasing beam intensity the proportion of 12N may be maintained at near 90% after each energy layer.
Conclusion: The investigation of delivery techniques which increase the feasibility of online range verification using PET is possible. Inverted energy sequences, increased dose rates, and spot reduced planning are recommended to improve the viability of on-line range verification of proton therapy using PET.

A motion-model guided 4D dose reconstruction for pencil beam scanned proton therapy

Type: Physics

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Aims: The common approach to 4D dose reconstruction in pencil beam scanned (PBS) proton therapy combines treatment log-files and real-time motion data to estimate the actual delivered dose from a single 4DCT acquired for treatment planning. The breathing pattern during treatment, however, may differ considerably from what is observed in such planning images in both amplitude and frequency. We introduce the use of patient-specific motion-models driven by surface surrogates to estimate time-resolved CT images for log-file 4D dose reconstruction, thus accounting for irregular patient breathing.
Methods: The correlation between external surrogates and anatomical deformations is modeled from the planning 4DCT using principal component analysis. Afterwards, this model is used to reconstruct the patient's full deformable motion from motion data acquired during treatment with an optical tracking system and to generate synthetic 4DCTs by warping the planning CT. The model was validated on three abdominal/thoracic patient data using leave-one-out cross-validation (LOOCV), where 4D doses reconstructed using the synthetic images were compared to those calculated on original 4DCTs. Moreover, for each patient, three fraction doses from amplitude-gated treatments (7 mm PTV margin adapted to individual case) with rescanning were reconstructed using motion traces and synchronized delivery log- files.
Results: The model validation showed comparable 4D dose distributions for the predicted LOOCV and original 4DCT with absolute dose differences >10% in less than 3% of the PTV for all cases. Inter-fractional differences in the reconstructed doses resulted in differences below 2.0% in CTV V95% (V95%≥97.7% for all fractions) and 2.9% in D5%–D95% (D5%–D95%≤10.6%), confirming the robustness of gated treatments against motion irregularity occurring during irradiation.
Conclusion: We have successfully implemented a retrospective 4D dose reconstruction workflow based on real-time motion data acquired during PBS proton treatments, thus considering both intra- and inter-fractional motion variability. For the studied clinical cases, an acceptable target dose coverage was maintained for all fractions.

IMPT dose painting for time evolved hypoxia using HX4-PET in HNSCC

Type: Physics

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Aim: This work aims to design a patient specific workflow for estimating dose escalation and exploring the potential of personalized adapted IMPT planning. We investigated a split-treatment approach for time-evolved hypoxic tumour sub-volumes at two distinct points during treatment; at baseline and after 9 fractions of radiotherapy.
Methods: HX4-PET images were used to delineate a hypoxic target volume (HTV) within the clinical target volume (CTV) with a tumour-to-muscle ratio >1.4. A non-linear conversion model was used to obtain voxelised partial oxygen pressure (pO2), which along with variable LETd, was used for the proton-based oxygen enhancement ratio (OER) calculation. The patient specific dose escalation factor to the HTV was defined using the calculated OER normalised to normoxic OER. Tumour control probability (TCP) was assessed for the split-treatment approach and evaluated against three plans; the delivered IMRT plan, a conventional IMPT plan and a hypoxia boosted proton plan based on baseline hypoxia. Additionally, normal tissue complication probabilities (NTCP) were taken into account to compare the clinical effectiveness of the plans.
Results: For a patient with T2N2b oropharyngeal squamous cell carcinoma (SCC), the hypoxic volume shrunk in size by 13.2% after 9 fractions along with a slight shift in position. Similarly, the functional information from PET indicated a lower boost of 10.6% for the shrunken HTV compared to an escalation of 12.5% to overcome the baseline hypoxia. A minimal increase in dose to the organs at risk was observed whereas an improvement of 10% was estimated in TCP with the split-treatment approach as compared to the conventional IMPT/IMRT plan. The dose escalated IMPT plan simultaneously reduced the mean doses to contralateral submandibular gland by 15.39 GyRBE, contralateral parotid by 2.8 GyRBE, and spinal cord by 13.75 GyRBE compared to the non-dose escalated IMRT plan.
Conclusion: By including spatially and temporally varying hypoxia during adaptive treatment planning an improved tumour control is achieved, while reducing doses to the organs at risk, compared to conventional IMRT plans for oropharyngeal SCC.

Clinical experience on replacing patient specific QA measurements with a complexity analysis combined with dose recalculations

Type: Physics

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Aims: Volumetric modulated arc therapy (VMAT) is associated with complex delivery systems and significant hardware burden. Dose rate modulation, collimator movement and gantry rotation have to be synchronized precisely. Pre-treatment patient specific quality assurance measurements (PSQA) ensure the correctness of the delivery; however, it demands a significant time allocation. The total time required for each PSQA is estimated to be 25 min (10 min preparation, 5–10 min measurement, 5–10 min evaluation). We reduced this by introducing a triage system to measure the most complex plans only. Here we report on our clinical experience with this new system.
Methods: In April 2022 we implemented a selection criteria for performing PSQA based on the mean MLC opening (MMO) of VMAT plans. This was realized with an in-house developed software based on the Eclipse Scripting API (ESAPI). Resulting from a retrospective analysis of 290 VMAT plans using 6 MV beams, we set the threshold MMO = 16.5 mm. Since then only plans with smaller MMO were verified with portal dosimetry (PD) and the gamma agreement index (GAI) is extracted with criterion 3%/2 mm. One in ten patients with MMO>16.5 mm is randomly selected for PSQA to guarantee the robustness of the workflow.
Results: In the period April–May 2022 we analyzed 244 VMAT plans for 142 patients and PSQA was required for 49 plans (20%). The VMAT fields below the MMO threshold had average GAI = 99.06% (range 89.8–100) and average MMO = 13.9 mm (9.6–16.4). An independent dose recalculation was done for all plans. Delta4 measurements were performed for two plans (0.8%) with MMO<16.5 mm and GAI<95% to fulfill our PSQA requirements. The randomly drawn plans had average GAI = 99.85% (99.3–100) and average MMO = 32.4 mm (22.9–43.0). The time saved in two months was approximately 80 h, of which 16–32 h of machine time.
Conclusions: We developed an in-house ESAPI software to select the VMAT plans requiring measurement based PSQA. The robustness of the approach was confirmed by the GAI between the plans selected for PSQA according to MMO or according to the random draw. The number of PSQA was reduced by 80% while ensuring a gamma passing rate>95% for all plans.

Optimization of the method for film dosimetry with EBT3 and EBT-XD Gafchromic films

Type: Physics

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Aims: Radiochromic films have been widely studied throughout the years, owing their popularity to their numerous advantages such as an unequalled spatial resolution. Nevertheless, their use is still unpractical resulting in an untapped potential. One of the drawbacks when it comes to film dosimetry is the stabilization time after the exposure, as well as the repeatability of the film readings. This study aims to optimize the protocol for accurate clinical dosimetry by studying the stabilization time and by identifying and reducing error sources during the scanning process. The properties of EBT3 and EBT-XD Gafchromic films were compared for doses from 0 to 10 Gy. The dosimetric system was composed of EBT3 and EBT-XD Gafchromic films, a V850 Epson flatbed scanner and the Mephysto software, which uses the red-channel to obtain the optical density. A clinical photon linac with a 10 MV energy beam was used for the irradiations. We compared calibration curves obtained 10 min, 30 min, 1 h, 12 h, 24 h, 36 h, 44 h and 7 days post-exposure. It was found that 10 min after the irradiation, we could obtain a dose uncertainty of 0.88% for EBT3 and 2.47% for EBT-XD, considering a scan time window of ±2 min and a strict procedure of scanning. From that result, it appeared that EBT3 films are more accurate at low doses than EBT-XD, although EBT-XD are still satisfactory to use on this dose range. The scan time should be strictly respected as a 5 min scan time difference increased the dose difference of more than 1%. Furthermore, the dose differences increased over time: calibration curves above 36 h post-exposure were less accurate, with an inaccuracy up to 4.15% for EBT3 7 days post-exposure. Additionally, we identified numerous parameters as error sources during the scan of a film. A scan procedure was defined with a repeatability of 0.04%. This study showed that accurate dosimetry can be achieved with a more convenient procedure: using a calibration curve at 10 min post-exposure, following a specific scan procedure, with an overall uncertainty below 1% for doses ranging from 0 to 10 Gy.

Leveraging scripting and automation to evaluate adaptive treatments on an Ethos accelerator

Type: Physics

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Aims: Adaptive planning statistics are key to quantify the benefits of this type of radiation treatment. Adaptive plans are generated on-couch for each treatment session, taking into account the patient's daily anatomical changes. Given the large amount of data generated by this procedure, automation is a key element to perform such an analysis. The

adaptive plans generated by the ETHOS system are transferred back to Eclipse, enabling the automated extraction of DHV data and plan parameters using ESAPI scripts.

The resulting data is then processed and analyzed in Python.

Adaptive and scheduled normofractionated plans for the pelvic region (prostate and rectum) are included for analysis. The adaptive plan is the plan of the day, while the scheduled is the reference plan, tailored only for the patient's initial anatomy. We perform a comparative analysis of the two sets of plans in terms of dosimetric indices and clinically relevant DVH points, providing insight in the benefit of the adaptive procedure.

Comparison of Tomohelical and VMAT plans for left breast irradiation with deep inspiration breath hold

Type: Physics

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Radiotherapy

Aim: Our department recently acquired a Radixact® machine, after years of practice on a conventional linac equipped with a respiratory gating system. The objective of this study is to compare our reference technique for left breast cancer treatment: VMAT with Deep Inspiration Breath Hold (VMAT-DIBH), with our new practice of Tomohelical in Free Breathing (TH-FB), and with what we hope to be able to do in a few months, Tomohelical in DIBH (TH-DIBH).
Methods: 15 left-sided breast patients were scanned in FB and in DIBH. Treatment plans were prepared in RayStation for the three techniques with prescription 50 Gy to PTV Breast and 60 Gy to PTV Boost_SIB in 25 fractions. First, we optimized a VMAT plan on the DIBH CT according our objective. Then the same optimization was repeated using a TH technique on both CTs. Helical beam parameters were 5 cm field width and a pitch value according to Chen et al. (Med Phys 2011). VMAT plans used 3 or 4 partial arcs. PTV coverage and homogeneity index (HI), and OAR DVH were compared with a t-test calculation (results significant at $p<0.05$).
Results: Breast PTV coverage is better for both DIBH techniques than for FB, whereas PTV boost coverage is similar for FB and DIBH techniques.

PTV HI is significantly better for TH-DIBH and VMAT-DIBH compared to TH-FB. For the OAR, left lung mean dose was 8 Gy, 7.7 Gy and 7.4 Gy for TH-FB, TH-DIBH and VMAT-DIBH, significantly better for VMAT-DIBH. Heart mean dose was <2.7 Gy for all techniques, significantly better with VMAT-DIBH. The left anterior descending artery mean dose is significantly better on TH-DIBH compared to TH-FB and VMAT-DIBH.

For right breast and right lung, the VMAT-DIBH gives significantly better mean doses. Treatment times are on average 259s, 276s and 122s for respectively TH-FB, TH-DIBH and VMAT-DIBH.
Conclusions: All three techniques optimized in the same TPS give acceptable results with an advantage for DIBH for PTV coverage and OAR sparing. Apart from the technical challenges for the implementation of TH-DIBH, delivery time could also be a limiting factor for the implementation of this technique.

SRS MapCheck for CyberKnife Machine QA

Type: Physics

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Aim: Cyberknife (CK) is a robotic image-guided system for stereotactic dose delivery (Accuray Incorporated, Sunnyvale, CA, USA) that requires specific QA including MLC (Bayouth test), iris aperture and Targeting Accuracy QA (TAQA) tests. Machine QA is currently performed using Accuray procedures and Gafchromic films. Patient-specific QA is done using the SRS MapCheck digital detector (Sun Nuclear). The aim of this study was to characterize the performance the SRS MapCheck for Cyberknife machine QA with the goal of replacing the use of film for daily QA.
Methods: For each test, a Precision (v 3.3) plan was prepared. For the MLC Bayouth test, reproducibility and induced-error tests were performed. For iris aperture QA, reproducibility and sensitivity were evaluated. For the TAQA, reproducibility was evaluated and film based TAQA measurements (considered as gold standard) were done for MLC, iris and cones to monitor sensitivity over time.
Results: Initial results show that leaf position deviation >0.5 mm was detected for the Bayouth test for both X1 and X2 banks (manufacturer tolerance <0.51 mm position deviation). However an unexpected fully closed leaf was not detected. For iris aperture, standard deviation of repeatability and reproducibility was below 0.1%. The digital detector could detect aperture deviations from 0.1 mm. Nevertheless, the reliability of the absolute value of the measured deviation has to be investigated.

Digital and Gafchromic film based TAQA tests gave similar results, below the 1 mm tolerance specified by Accuray.
Conclusion: We conclude that the SRS MapCheck could be a reliable tool for daily constancy checks including MLC Bayouth (replacing picket fence), and TAQA. However, the lower detector resolution compared with Gafchromic films means that it cannot be used for all machine QA tests. Further investigations are in progress about the accuracy of the absolute diameter determination for iris aperture QA.

First Accuray CyberKnife treatment with Raystation treatment planning system and Raycare oncology information system: experience sharing

Type: Physics

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Aims: The first treatment using the Accuray Cyberknife system with Raysearch treatment planning and oncology information system was recently delivered at La Clinique-Générale-Beaulieu.

We present here the steps followed for treatment preparation, issues encountered and controls performed in the setup of this new treatment workflow.

Reference images were acquired using the same protocol as the one used for Precision planning.

Plan was made with Raystation 11A (RS) choosing the Skulll motion synchronization technique dedicated for intracranial lesion. The align center of Precision is called Isocenter in RS. As there is no instruction on how to place this point in RS, nor dedicated "align" window, it was though placed according to Accuray recommendation, adapting these coordinates and checking the setup DRRs views.

The beam was defined using this point as "isocenter" and the node set "head MLC". Plan optimization was done as usual putting objectives and constraints on PTV and organs at risk. No structure was blocked in entrance and/or exit, since it is not available in RS 11A. Besides, minimum monitor units per beam can't be set, and an a priori adapted number of nodes has to be chosen to ensure the conversion process. Once approved, plan was sent to the IDMS data management system. DRR's were generated in Precision. Dose distribution of imported plan can't be seen in Precision. QA plan was then calculated in RS and sent to the IDMS, paying attention to registration between the PTV and the QA detector, previously imported in RayPhysics. Fiducial tracking algorithm was used for the QA delivery. In parallel, end to end (E2E) plan, generated in RS, was done with the combination MLC/skull, to check the skull patient treatment tracking algorithm. Results were below 1 mm Accuray recommandations and gave similar results as E2E Precision plan.

A fake plan was previously sent and run to ensure the correct transfer of the irradiation parameters between RS and IDMS.

Finally, the patient's treatment was scheduled in RayCare and transmitted via RayTreat to the UCC. The treatment was safely delivered on the patient and the delivered beam information was successfully retrieved in this OIS.

Type: Technicians

The evolution of the role of RTTs in the context of thermo-radiotherapy

Type: Technicians

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Aims: Since July 2021, our institute offers hyperthermia (HT) as an adjunct treatment to radiotherapy in order to enhance radiation dose efficacy. The available HT technology (ALBA hyperthermia, Med-Logix srl) exploits extracorporally placed antennas, emitting radiofrequency electromagnetic fields to heat the tumor region up to 40–43 °C for 1 h. HT enhances the efficacy of radiotherapy if delivered within a short time interval (ideally <60 min) after irradiation. This contribution describes the role of the Radiation Therapy Technicians (RTTs) in guaranteeing a smooth clinical workflow for HT treatments, being crucial for its efficacy.

Methods: RTTs are involved in the following main tasks during the HT treatment: 1) positioning the patient in the HT room, limiting the time interval between radiotherapy and HT delivery; 2) measuring the temperature through thermocouples positioned on the patient's skin or in intracavitary probes; 3) monitoring the patient throughout the treatment; 4) controlling the machine parameters (e. g., power, phase, amplitude, water bolus temperature) in order to obtain the therapeutic temperature while maintaining patient comfort.

Results: To date, more than 20 patients have been treated with thermo-radiotherapy and no adverse event has been reported. The primary HT team included 4 RTTs, who are progressively translating their knowledge and experience to other colleagues. Moreover, research studies are being designed to integrate Magnetic Resonance Imaging (MRI) in the workflow of HT, allowing to improve HT treatment planning and treatment outcome verification.

Conclusion: The role of RTTs has seen a radical evolution with the installation of HT technology. In our experience, RTTs must undergo proper training and gain sufficient hands-on experience to deal with the complexity of the clinical workflow of thermo-radiotherapy.

Performing a risk analysis of processes in the radiation oncology department

Type: Technicians

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Aim: As part of the recertification process, an annual risk analysis must be performed. To check the processes, a method is sought that examines each individual step for possible errors. This method should always be structured in the same way, to ensure a safe and uncomplicated analysis. Our aim was to evaluate as many clinically relevant processes as possible throughout the department using this method, in order to improve the quality of radiotherapy treatment and patient safety in the future.

Method: HFMEA ("Healthcare Failure Mode and Effect Analysis") is a quality insurance method used in health care. It describes a step-by-step evaluation and structuring of diagnostic and therapeutic methods with the aim of achieving the desired clinical result. Because the HFMEA method is extremely time-consuming, we decided to use the HFMEA-light method for our study. This light method examines the possible risks and causes of the most critical steps in a process. In this study, the process '1. Chart-Check' was selected. For the risk analysis, we developed an Excel sheet which listed 65 processes, for which the following criteria were to be answered individually by each MTRA machine manager (MTRA_GV): possible errors and causes, severity (ranking from small (1) to catastrophic (4)) and frequency (ranking from annually (1) to weekly (4)). We subsequently calculated the Risk Priority Number (severity x frequency) for each process step. Based on the filled-out Excel tables, the researcher held seven interviews, one with each MTRA_GV.

Results: Through the risk analysis, the dangers in the '1. Chart-Check' process could be identified and prioritized. Based on all Risk Priority Numbers, we were able to identify a list of the 10 most critical process steps. After prioritization, we discussed these process steps among all MTRA_GVs, which led to the development of a number of improvement measures.

Conclusion: Our study analyzed the possible sources of error for the '1. Chart-Check' and developed solutions to minimize these. As a result, this method has been accepted by the employer and established as the department's standard tool for risk analyses.

A comparison between Surface Guided Radiation Therapy and tattoo-based patient positioning

Type: Technicians

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Aims: Since 2018, Surface Guided Radiation Therapy (SGRT) replaced tattoo-based laser alignment for patient setup at our institute. The aim of this study is to evaluate the accuracy of the SGRT workflow by comparing it to the one previously used, the well-established tattoo-based approach.
Methods: We selected 40 breast cancer patients who underwent boost on the tumor bed (2 Gy/fract for 6–8 sessions). Skin tattoos were used for setup in 20 patients, whereas SGRT with the Catalyst (C-Rad) was applied in the remaining 20 patients. For each patient, the residual setup error was quantified as the median displacement of the surgical clips between the kV 2D images acquired after patient setup and the corresponding Digital Reconstructed Radiographs from the planning Computed Tomography.
Results: No significant difference was found in the lateral, antero-posterior, cranio-caudal, and 3D residual errors between the two techniques (Wilcoxon test, $p > 0.05$). The median (interquartile range) 3D error was 0.37 (0.22) mm and 0.40 (0.35) mm with SGRT and tattoo-based approach, respectively. Both approaches had good accuracy, with median errors below the clinical threshold used for patient setup acceptance (i. e., 0.50 mm). The 3D error obtained with SGRT showed a lower dispersion (Ansari-Bradley test, $p = 0.02$), suggesting better reproducibility with SGRT with respect to the tattoo-based approach.
Conclusion: Patient setup with SGRT showed high accuracy, comparable to the previously used tattoo-based method, and good reproducibility. Moreover, in the clinical practice, the SGRT method improved the patient positioning workflow by exploiting the whole thorax and arms surface and reducing the physical contact between the technician and the patient.

Generating synthetic contrast enhancement from pelvic non-contrast PET/CT with artificial intelligence algorithm

Type: Technicians

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Aims: The use of iodinated contrast [IC] in diagnostic imaging is a common modality that improves tissue, vascular and lymph node visualisation, and the quality and accuracy of the interpretation of the medical imaging examination (X-ray computed tomography [CT] or PET-CT). However, this use is limited in some patients.

ICs are contraindicated in patients with renal failure, allergy to iodinated contrast or dysthyroidism. Failure to use IC may result in a loss of opportunity for these patients in the interpretation of their examination.

The objective is to develop an algorithm to synthetically generate vascular contrast, focusing on the pelvic region from non-injected CT scans.
Method: Matched and unmatched PET/CT scans with and without CI were collected from 128 patients. CT slice volumes from the pelvis (between the upper plateau of L4 and the lower limit of the ischium) were extracted and anonymised from DICOM to NIFTI format.

We use initialy only 43 image sets were selected and integrated, representing a total of 16,000 CT-Scanner images.

We put in competition two training algorithms, which are the convolutional network U-Net, and the "Cycle Generative Adversarial Network "or "Cycle GAN ", using the computing power made available by AWS thanks to the cloud computing.
Results: Encouraging preliminary results, after seven computational epochs, allowed automatic detection of femoral and iliac arteries using the GAN cycle.

Only tissue grey level differentiation could be achieved using the U-NET convolutional network.
Conclusion: Initial results were very promising and allowed automatic detection of the femoral and iliac arteries after only 7 epochs. A longer training time and an enrichment of the dataset with new and better data will improve these first results. In clinical routine, such an optimised tool will allow synthetic vascular contrast to be obtained in less time, reduce radiation protection, eliminate allergic risk, improve patient comfort without loss of chance and induce public health savings related to excessive use of CI.

How to prevent a cyberattack in radiotherapy? Measures to implement

Type: Technicians

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Aim: Nowadays, healthcare organizations are a prime target for cyberattacks. Oncology services are among those that can suffer the most, as they are very susceptible to the consequences of such attacks on patient care procedures. Preventing measures can avoid losing important data, business disruption, financial expenses for restoring systems and files, and reputation damage.
Materials/Methods: A review of prospective literature on cyberattacks with the keywords: "radiotherapy", "cyberattack" and, "cybersecurity" was performed. The presented measures were based on scientific articles, published since 2016, most of them associated with cyberattacks on similar institutions. Such prevention measures were also described according to their institutional needs.
Results: A prevention plan requires a change in strategies, tactics, and culture around cybersecurity in radiotherapy, which are challenging in themselves. Before implementing the prevention measures, there was a high susceptibility to several consequences if a cyberattack would have happened because a radiotherapy service can easily have to stop its operations due to the loss of patient data. With the implementation of such measures, there is the possibility of reducing risky behaviors and increasing cybersecurity on the institutional level.
Conclusion: Healthcare is one of the lower industry spenders on IT. Nevertheless, their data is one of the highest valued by hackers, so it is an ideal environment for cyberattacks. Organizations providing oncology care should be alerted to the possibility of cyberattacks. They should develop processes to reduce the impact of this activity on these essential services.

Clinical implementation and site-specific workflow for free-breathing abdominal SBRT with 1.5T MR-Linac

Type: Technicians

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Aims: Abdominal target are subject to respiration and internal motion during treatment. This work describes the implementation and initial experience of MR-guided radiotherapy on the 1.5T MR-Linac for free breathing SBRT abdominal moving target from an RTT perspective including the positioning and setup procedures, treatment delivery workflow, and patient compliance.
Methods: Ten patients with liver and adrenals metastasis received daily adaptive radiotherapy on an Elekta Unity MR-Linac. Motion was managed creating an ITV from the 4DCT and 4DMR simulation using an in-house immobilization system.

Treatments of 6 patients were carried out with the adapt-to-position (ATP) workflow and 4 patients were treated with the adapt-to-shape (ATS) approach. Treatment delivery were performed with visual guidance of the live sagittal and coronal Cine-MRI coupled with audio feedback when it's necessary to reproduce a manual gated delivery. Patient compliance was assessed using an in-house developed questionnaire to document their treatment experience and tolerance.
Results: The in-house immobilization system decreases the respiratory movement and improve the treatment accuracy. Only two patients reported some MR-related complaints (e. g. uncomfortable positioning and long treatment session).
Conclusion: The Elekta Unity MR-Linac enables a direct visualization of target motion during treatment delivery allowing to deliver safe free breathing SBRT plans while waiting the automatic gating technology that will be implemented in a near future.

Plan of the day adaptive radiotherapy in prostate cancer

Type: Technicians

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Aims: Development of a protocol for Development of a protocol for adaptive radiotherapy dependent on bladder filling.

A protocol was developed for "plan of the day" technique using image-guided radiotherapy (IGRT) and based on VMAT plans. Endpoints of analysis were PTV coverage, bladder and rectum sparing) in different states of bladder filling. In short: Patients have two CT-scans, one with a full bladder and one with a half-full bladder. 2 plans are calculated. The maximum number of sessions with a half-full bladder and still allowing a reasonable distribution of doses for the PTV, the bladder and the rectum is determined from the dosimetry. On the linear accelerator, the plan of the day is selected and delivered, based on the contour and actual bladder filling (half full/full) using a CBCT image. The plan provided for optimal bladder filling is preferentially used. The number of irradiations with the plan intended for a half bladder filling is checked and stopped when the maximum number of possible sessions is reached. At the end of therapy the dose actually delivered to the PTV/bladder/rectum is recalculated by the dosimetry team.
Results: Preliminary results will be presented. In the first patient the plan with partially filled bladder was allowed to be delivered for 7 of 33 fractions in order to keepbladder and rectum dose within the accepted constraints. During treatment, full bladder conditions were achieved for 28 fractions, in 5 fractions it was necessary to resort to the partially-filled bladder plan-of-day. Dose evaluation of bladder/rectum is shown for full/partially filled case.
Conclusion: Our plan of the day protocol is feasible. Dosimetric analysis of the first patient after end of the treatment regimen showed only minimal dosimetric differences when two treatment plans are applied. Results of additional patients will be presented as SASRO.

Optimization of the treatment time of patients in radiation oncology

Type: Technicians

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Aims: The Centre Hospitalier Universitaire Vaudois (CHUV) is trying to optimize the treatment time of patients in radiotherapy. An analysis of actual processing times was carried out. The study considers the time required for patient care by radiotherapy technologists (RTT) among other factors determining the total duration of treatments.
Methods: The analysis of the intervention time for treatment was carried out on three machines: a linear accelerator (LINAC) and two Tomotherapy devices of different generations. Data was collected over three days for the LINAC and four days for the Tomotherapy equipment, in January and March 2022. Activities under analysis were: patient installation; imagery; fusion of images; irradiation; and evacuation of the treatment room. In total, data was collected and analyzed for 52 complete treatments on the LINAC and 48 complete treatments for each of the Tomotherapy machines.
Results: This study identified human, organizational and technological factors influencing the total duration of the treatment time. On average, the time required for a complete treatment, ie from patient entering the room to leaving, for the LINAC is just about 16 min whilst it is 15 and 18 min for Tomotherapy. Total treatment time varies from 10 to 35 min. Depending on equipment, time distribution for each activity varies between 18% and 22% for installation, 7% and 17% for imaging, 12% and 21% for fusion of the images, 29% and 40% for irradiation; and finally, between 11% and 14% for the release of the room.
Conclusion: Results reveal the potential for optimizing treatment time by RTT is essentially limited to installing the patients and, to a lesser extent, freeing the room. The optimization of total treatment time largely depends on medical and administrative decisions made prior to RTT's intervention with patients. Alternate ideas for optimization are proposed.

Patient specific neural networks for contour propagation in online adaptive radiotherapy

Type: Technicians

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Aim: In online adaptive radiotherapy (ART), the treatment is reoptimized each fraction based on a daily image so that radiation can be delivered more precisely. Therefore, daily contours are needed, which can be obtained by automatic segmentation (AS) or image registration (IR). This is typically followed by manual adjustments, considered as a bottle-neck for clinical introduction of ART. State of the art AS uses neural networks (NN) trained on a large dataset. Contrarily, IR relies on a single, but highly relevant example. In this work, we train patient specific NN (PSNN) to combine information of a large dataset with the highly relevant reference CT for contouring of daily CTs in proton therapy.
Method: The methods were evaluated on 5 lung cancer patients with a reference and 9 repeated CTs with manual contours of the relevant OARs. A 3D UNet was trained to segment the OARs on another dataset with 110 labels, yielding a pretained NN (PNN). This NN was further fine tuned for each patient solely on the reference CT, yielding 5 PSNNs. We compared these NN to rigid (RIR) and b-spline deformable IR

(DIR) using the surface dice (SD) between the propagated and manual contours. To assess the dosimetric impact of using un-corrected contours, we reoptimized the plan on the daily CTs with propagated OAR and manual CTV contours. These plans were compared to the ones reoptimized on all gold standard manual contours using the DV2, i.e the contour volume fraction where the dose difference between the plans is higher than 2% of the prescribed dose.
Result: Fine tuning the PNN on the reference CTs increases contour quality (Table). The dose difference between the reoptimized plans is already small using non-perfect contours (RIR) and is even lower for DIR and PSNN.
Conclusion: Patient specific fine tuning of NN increases their accuracy and results in similar performance as DIR. Further, our results show that fast PSNN and DIR contours of OARs without time-consuming manual adjustments are suitable for reoptimizing plans in ART for lung cancer.

Table 1

	SDOAR [%]	DV2OAR [%]	DV2ctv [%]	Time [s]
PNN	81.0	2.5	4.7	11
PSNN	89.4	1.7	4.9	11
RIR	69.1	2.6	5.5	16
DIR	90.3	1.5	4.9	115

Improving initial setup accuracy with the use of SGRT in the treatment of localizations in the upper leg with the use of Bolus.

Type: Technicians

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Aims: Patients with tumors in the upper leg can be difficult to set up due to variation in tumor location, use of bolus, and difficulties in standard limb immobilization. The aim of this study is to improve setup accuracy and reproducibility with a comprehensive use of Surface Guided Radiation Therapy (SGRT).
Method and materials: AlignRT was used for the initial positioning of 9 patients with upper leg tumors treated over 152 fractions. Bolus was included in the setup for 5 patients. For 2 of these bolus setups, the original body contour without bolus was used as a Reference Surface for the initial setup with AlignRT. For the other 3 setups, a Reference Capture was acquired without bolus, once the setup had been completed and confirmed using a CBCT. This new reference was used for the subsequent fractions for the initial setup before adding the bolus. The remaining 4 setups were treated without bolus and using the original body contour as the Reference Surface. In all setups, daily imaging was used to verify positioning before treatment. The residual shifts (in all 6 directions) were recorded, and the number of repeated images.
Results: The average residual shifts obtained from image matching in each direction and the # of fractions with repeated imaging are reported in Table 1.
Conclusions: Due to a decrease in the average residual shifts after imaging (most dramatically in the Roll direction), it can be inferred that using a new weekly Reference Capture with SGRT to position patients with bolus on the leg might improve setup accuracy. Most importantly, no repeat images were necessar for the initial patients. Patient positioning problems due to change in tumor size or swelling may be reduced by taking a new Reference Capture on a weekly basis.

Table 1 The # of patients included in each category is in brackets

VRT (cm)	LNG (cm)	LAT (cm)	Pitch (°)	ROLL (°)	RTN (°)	# of Fx with repeated images
0.56	0.33	0.30	1.04	1.33	1.30	1 Setups with No Bolus (5):
0.49	0.66	0.67	0.77	1.91	1.38	7 Setups with Bolus (Body Contour) (2):
0.47	0.40	0.40	0.88	1.27	1.20	0 Setups with Bolus (New Ref.) (2):

Treatment and time management in MR-guided radiation therapy

Type: Technicians

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Aims: Since 2019, over 400 patients have been treated using the MRIdian system (Viewray) at the University Hospital of Zürich. MRI technology allows daily online treatment adaptations to be performed. The aim of this study is to evaluate the time efficiency of a fully adaptive MR-guided workflow.
Methods and materials: Since January 2022, the treatment times of 50 patients treated on MRIdian with various fractionations were recorded.

The following times were documented:

- Patient was initially positioned on the treatment couch Low and High Resolution MRI scans were started Physician began contouring
- Physicist began optimizing the new adaptive plan QA was started
- Next High Resolution scan was started First treatment beam started
- Last treatment beam finished
- Patient was taken off the treatment couch

The total treatment time was recorded from when the patient was positioned on the couch to when they were taken off the couch after treatment.
Results: The median total treatment time was 62 min. Re-contouring and initial patient positioning required the most time, with a median of 13 min per adaptation each. Further results are displayed in Table 1:
Conclusions: With the current workflow for daily adaptive treatments on the MRIdian, the median treatment time is 62 min. Re-contouring is about four minutes longer for the first treatment when compared to subsequent fractions. This can be due to changes in patient anatomy between the simulation and first treatment, and from a better understanding of deformation quality of OARs after the first adaptation. Further development and improvements in automatic segmentation of OARs will be crucial for more time efficient workflows.

Table 1 The median, minimum and maximum time values displayed in minutes

Total Setup Time:	Contouring Time:	Optimization Time:	Beam On Time:	Total Tx Time:
All fractions:				
00:13	00:13	00:08	00:12	01:02 Median:
00:04	00:03	00:02	00:04	00:41 Min:
00:40	00:38	00:33	00:47	02:00 Max:
Only first day fractions:				
00:13	00:17	00:10	00:11	01:07 Median:
00:07	00:03	00:04	00:07	00:45 Min:
00:24	00:36	00:22	00:23	01:38 Max:

Comparison of skin marks and surface imaging for breast radiotherapy patient positioning

Type: Technicians

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Aims: Our service has two different machines that are used for breast radiotherapy, each with its own daily patient positioning system. On one machine, patients are set up with the aid of skin marks and lasers. On the other machine a surface imaging system is used, with no skin marks after the first treatment fraction. We compared the reproducibility and precision of these two setup methods for a sample of breast and loco-regional breast patients.

Registration values after pre-treatment imaging were evaluated for 20 patients (10 patients for each machine) and 500 treatment sessions.

Translational shifts in the longitudinal, lateral and vertical directions were compared to the fixed objective and limit thresholds that have been established for our practice. Similar registration values were obtained regardless of the setup system used.

Overall, on image analysis of the daily setup CT, the patient's position better matches the position of the planning CT for the surface repositioning system.

The surface repositioning system covers a large surface to be repositioned and enables an online check of the arms position. However, the correct use of this system requires significant training, and understanding of the technologist teams. In comparison, skin marks are time consuming to maintain and add a dimension of stress and discomfort to the patient. In conclusion, the use of the surface repositioning system is advantageous for the patient as well as for the precision of the patient setup.

Seminal vesicles move: displacement in image-guided radiotherapy of prostate cancer based on gold marker coregistration

Type: Technicians

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Aims: Interfractional motion of the seminal vesicle (SV) is known to be larger than the motion of the prostate (P), which affects SV dose coverage with the current clinical planning limit. This study aims to evaluate the dose coverage of SV when interfractional motion is considered and to determine whether the clinical planning margin for SV is appropriate for the treatment of intermediate- to high-risk prostate cancer with intensity-modulated radiotherapy.
Methods: Nine patients with prostate cancer receiving curative radiotherapy with a total of 63 daily Cone-beam CT images (CBCT), using gold markers, were reviewed. On CBCTs prostate and SV were contoured by a physician using rigid registration and matching the daily prostate contour to the planned prostate contour. Each SV contour was transferred to the planning CT to create an internal target volume

(ITV). The PTV-margin for the SV was 8 mm in every direction. The D99% of the ITV and the percentage volume of the ITV that received the prescribed dose were evaluated for each patient. We also examined the geometric overlap between the ITV and the planning target volume (PTV) and determined the margins that would be required to achieve 100% geometric coverage of the SV with daily image-guided radiotherapy fused to the gold markers.

Results: Mean coverage of the ITV with D99% was 83.1% ±16.8% of the planned D99% of the PTV (P+SV). The mean volume of ITV receiving the prescribed dose was 99.7% ±0.9%. The average percentage volume of ITV that overlapped with the clinical PTV was 96.7% ±3.5%. On average the SV were not covered by the PTV as planned for 3 fractions per patient using an 8 mm margin for PTV. To achieve 100% geometric conformity of ITV and PTV a planning margin of 10 mm for the SV would be needed, especially in the superior and posterior directions.

Conclusions: Interfractional observed SV motion was larger than interfractional motion of the prostate when gold marker matching was used. The planning margin for SV should be extended superiorly and posteriorly by 2 mm to improve ITV coverage, especially with large daily displacement due to coordinate changes of gold markers.