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<td>Restricted to other programme participants (including the Commission Services)</td>
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**LIST OF ABBREVIATIONS AND DEFINITIONS**

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<td>CT</td>
<td>Computed Tomography is a medical imaging technique using a large series of two-dimensional X-ray images.</td>
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<td>CTV</td>
<td>Clinical Target Volume is a volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease at a certain probability considered relevant for therapy.</td>
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<td>D</td>
<td>Absorbed dose is a measure of the energy deposited per unit mass of medium by ionising radiation, and so has the unit Gy.</td>
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<td>DIssoE</td>
<td>Isoeffective dose is the absorbed dose that delivered under the reference conditions would produce the same biological effect in a given system as the actual treatment, all other conditions being the same.</td>
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<tr>
<td>Dref</td>
<td>Dose of the reference radiation quality selected for the definition of the RBE.</td>
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<tr>
<td>DRR</td>
<td>Digitally reconstructed radiograph</td>
</tr>
<tr>
<td>Dtest</td>
<td>Dose of the test radiation quality used for the definition of the RBE.</td>
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<tr>
<td>DVH</td>
<td>Dose-Volume Histogram is a concept used in radiation treatment planning.</td>
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<td>FDG</td>
<td>Fluorodeoxyglucose is a radiopharmaceutical used in PET imaging.</td>
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<tr>
<td>fMRI</td>
<td>functional Magnetic Resonance Imaging is a type of specialised MRI scan measuring the hemodynamic response (change in blood flow) related to neural activity.</td>
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<tr>
<td>GTV</td>
<td>Gross Tumour Volume is the gross demonstrable extent and location of a tumour.</td>
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<tr>
<td>Gy</td>
<td>Gray is the name of the special unit of absorbed dose of ionising radiation, i.e. the absorption of one joule of ionising radiation by one kilogram of matter.</td>
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<td>ICD-O</td>
<td>International Classification of Diseases for Oncology is a domain specific extension of the International Statistical Classification of Diseases and Related Health Problems for tumour diseases. This classification is widely used by cancer registries.</td>
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<tr>
<td>ICRU</td>
<td>International Commission on Radiation Units and Measurements is a standardisation body set up in 1925 by the International Congress of Radiology.</td>
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<tr>
<td>IMRT</td>
<td>Intensity-Modulated Radiation Therapy is an advanced type of high-precision radiation therapy technique.</td>
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<tr>
<td>Interfraction</td>
<td>Occurring between treatment sessions</td>
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<tr>
<td>Intrafraction</td>
<td>Occurring within a treatment session</td>
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<tr>
<td>ITV</td>
<td>Internal Target Volume is defined as the CTV plus a margin which takes into account uncertainties in size and shape of the CTV and its position/movements within the patient.</td>
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<tr>
<td>LET</td>
<td>Linear Energy Transfer is a measure of the energy transferred to material as an ionising particle travels through it.</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging is a medical imaging technique using a powerful magnetic field.</td>
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<tr>
<td>MRI-FLAIR</td>
<td>Magnetic Resonance Imaging FLuid Attenuated Inversion Recovery is a pulse sequence (inversion recovery technique that nulls fluids) used in MRI.</td>
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<td>Term</td>
<td>Definition</td>
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<tr>
<td>OAR</td>
<td>Organ At Risk or critical normal structures are tissues, which if irradiated could suffer significant morbidity, and thus might influence the treatment planning and/or the dose prescription.</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography is a medical imaging technique using pairs of gamma rays emitted indirectly by a positron-emitting radionuclide.</td>
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<td>PET-CT</td>
<td>Positron Emission Tomography and Computed Tomography is a medical imaging device which combines in a single gantry system both a PET and a CT.</td>
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<td>PRV</td>
<td>Planning Organ at risk Volume is, in analogy with the PTV, a geometrical concept considering uncertainties and variations in the position of organs at risk during treatment.</td>
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<tr>
<td>PTV</td>
<td>Planning Target Volume is a geometrical concept introduced for treatment planning and evaluation. It is the recommended tool to shape dose distributions to ensure that the prescribed dose will actually be delivered to all parts of the CTV, with a clinically acceptable probability, despite geometrical uncertainties such as organ motion and set-up variations. It is used for dose prescription and reporting.</td>
</tr>
<tr>
<td>RBE</td>
<td>Relative Biological Effectiveness is defined as the ratio of a dose of a reference radiation quality to the dose of the test radiation quality required to cause the same biological level of effect, all other conditions being the same.</td>
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<tr>
<td>RVR</td>
<td>Remaining Volume at Risk is the volume that is within the imaged region of the patient, and outside all delineated OARs and CTVs.</td>
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<tr>
<td>SOPB</td>
<td>Spread-Out Bragg peak is an overlap of several pristine Bragg peaks at staggered depths.</td>
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<tr>
<td>SUV</td>
<td>Standardised Uptake Value is often used in PET imaging for (semi-)quantitative analysis of dynamic data. It is useful for a simple analysis of FDG images, e. g. to monitor the progress of disease during cancer therapy.</td>
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<td>TNM</td>
<td>Classification of Malignant Tumours is a cancer staging system that describes the extent of cancer in a patient’s body. T describes the size of the tumour and whether it has invaded nearby tissue; N describes regional lymph nodes that are involved; M describes distant metastasis (spread of cancer from one body part to another).</td>
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<tr>
<td>TPS</td>
<td>Treatment Planning System used in radiation therapy for planning the doses in the tumour and the surrounding healthy tissue (critical organs).</td>
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<tr>
<td>TRiP</td>
<td>TReatment planning for Particles a treatment planning system for ion therapy developed at GSI and used at HIT, Germany.</td>
</tr>
<tr>
<td>TV</td>
<td>Treated Volume is the volume of tissue that receives at least the dose specified by the radiation oncologist in charge of the patient and considered as appropriate to achieve the goal of the treatment within the bounds of acceptable complications.</td>
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<tr>
<td>UICC</td>
<td>International Union Against Cancer is a non-governmental organisation dedicated exclusively to the global control of cancer.</td>
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<tr>
<td>VOI</td>
<td>Volume Of Interest is a generic term that can be used to refer to any volume that needs to be identified. The GTV, PTV, and OAR are examples of specifically-named VOIs.</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation is a specialised agency of the United Nations that acts as a coordinating authority on international public health.</td>
</tr>
<tr>
<td>W1soE</td>
<td>Weighing factor which takes into account the effects of all factors that could influence the outcome (mainly, dose per fraction, overall time, dose rate and radiation quality). Multiplication of weighing factor with absorbed dose results in the isoeffective dose.</td>
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PUBLISHABLE SUMMARY

Outcome assessment is crucial for understanding and improving current and upcoming treatment strategies. Outcome assessment in the field of hadron therapy will mainly imply analysis of local / regional relapses and treatment related side effects. Given the heterogeneous dose distribution delivered by proton or carbon ion beams, outcome assessment will be challenging and will make additional efforts in comparison to conventional photon beam radiotherapy necessary. Relevant aspects for outcome assessment in hadrontherapy include dose assessment and recalculation, dose-volume histogram analysis (based on standardized of target and organs at risk definitions), dose-effect analysis (by correlating dedicated dose parameters to specific events such as local recurrence) and multimodality imaging (morphological and topographical depiction of tumour and recurrence, visualisation of tumour / recurrence biology, visualisation of tumour response during therapy, visualisation of dose delivery). Finally an exemplary CRF is presented.

1. INTRODUCTION

The use of proton or carbon ions in radiation therapy (RT) will likely lead to highly individualized treatments. The outstanding physical characteristics of proton or carbon ion beams will allow for high dose delivery to the target volume (or even dose escalation within the target) while sparing the surrounding healthy tissues. This aspect may be especially advantageous in clinical situations with localized, bulky, not operable, radioresistant/hypoxic tumors with complex anatomical topography, where the target and the OAR are in direct proximity. Local/regional control is the priority. Such treatments will result therefore in highly heterogeneous dose profiles with areas of (high-) dose-peaks and areas of sharp dose fall offs. These considerable fluctuations of the dose distribution within the patient will be followed by varying biological effects at different sites. Moreover carbon ion beams deliver a higher equieffective dose (relative to the physical absorbed dose) in the spread-out Bragg peak area – that is supposed to encompass only the GTV and CTV(s). Additional challenges may occur due to topographical changes by tumour shrinkage, organ movement etc. In such cases dose prescription (and dose assessment by) to conventional dose points will hardly sufficiently reflect these complex procedures (WP2.5). Thus, one of the major challenges in proton and carbon ion RT will be how to analyse and compare relevant dose and volume parameters and their corresponding spatial dose distribution to correlate with both tumor- and OAR outcome.

A better understanding of tumour local/regional failure (LRF) patterns will help to evaluate the value of ion beam -therapy comprehensively in 3D and 4D.

Local treatment failure may occur in different conditions:
- planned underdosage of part of the CTV/PTV to protect OAR
- unexpected CTV/PTV underdosage due to organ motion, weight loss, tumour shrinkage...
- unexpected CTV/PTV underdosage due to setup errors, delineation error, unidentified target volume...
- global or partial CTV/PTV radioresistance (biological heterogeneity)
- inadequate radiobiological models (e.g., for RBE evaluation)

Radiobiological mechanisms that affect — or are suspected to affect — the outcome after RT may be classified as tumour burden, tumour cell proliferation and hypoxia. Specific radiotracers were developed to investigate those hallmarks of cancer using PET imaging.

On the other hand, toxicity related to the prescription has to be precisely analyzed to be correlated with dose deposition in regard with OAR topography. Given that it is extremely difficult to obtain pathological samples of human normal tissue after irradiation for histological and biological analysis and for longitudinal examination, it is important to establish in vivo functional and molecular imaging as a biomarker for early assessment and prediction of delayed or late organ dysfunction.

Dose and volume analysis will need comprehensive clinical research by linking dose-volume parameters to patient related events assessed by clinical investigations, modern morphological and functional imaging or
biological markers leading to dose-effect relationships. The predictive value and clinical relevance of dose and volume parameters will be in the centre of attention.

2. EXCURSUS: EXPERIENCE FROM IGABT

The scientific background of image-guided adaptive brachytherapy (IGABT) – a somehow comparable high precision and small volume treatment technique - may serve as a role model. In IGABT the radio-oncologist is confronted with similar challenges in terms of heterogeneity of the dose distribution and sharp dose fall off. First insights on dose-effect relationships were derived from connecting repetitive imaging, image-guided treatment planning, biology related adaptive target concepts and clinical outcome. By creating specific target volumes according to the potential tumour load and tumour response patterns (initial GTV at diagnosis, GTV at the start of brachytherapy, high-risk clinical target volume – HR CTV, intermediate-risk target volume) a significant dependence between certain – biologically weighted - dose values and their probability for achieving local tumour control could be demonstrated. It was shown that if a D90 ≥ 87 Gy for the HR CTV is applied, a local tumour control rate greater than 95% is achievable [3, 4]. Further topographic and dosimetric analyses revealed different patterns of LRF by directly linking low dose regions to the subsequent areas of failure. Within a matched-pair analysis significant differences in various dose parameters, which allowed for assessment of the heterogeneous dose distribution within the target volume (“D100, D98, D90, D50, mean point dose – MPD”), were shown between patients with a local recurrence and patients in continuous complete remission.[5] Similarly, first dose-effect relations could be observed for the assessment of late toxicity. The dose to specific small volumes was shown to predict the onset of certain side effects (e.g. rectal bleeding) by correlating dose with clinical symptoms and endoscopic findings. [6] Dose effect analysis demonstrated a significant dependence between rectal and urinary side effects grade 2-4 and the D2 cm³. The corresponding ED10 values were 78 Gy (rectum) and 101 Gy (bladder). Overall, actuarial incidence rates for G3/G4 side effects were 2% for rectum and 4% for bladder.

3. IMPORTANT ASPECTS OF OUTCOME ASSESSMENT IN CIRT BASED ON THE EXAMPLE OF SKULL BASE CHORDOMAS

An interesting example to raise hypothesis on pattern of tumor relapse and “toxicogenesis” in hadron-therapy are skull base chordomas. Skull base and cervical spine chordomas (SBCSC) are rare but locally aggressive and relatively radioresistant mesenchymal tumors surrounded by numerous OAR that constrain the therapeutic window.[7-10]

SBCSC are usually treated with a combination of radical surgery and particle therapy. A clear relationship between median (biologically weighted) delivered dose and local control probability was evidenced (Figure 1). Doses ranging between 25 and 60 Gy are purely symptomatic [11, 12]. Protontherapy is well suited due to the rapid fall off of the dose at the distal end of the Bragg peak and at its lateral edges – that may spare critical structures and permit a dose escalation on tumour volumes [13-15]. CIRT was fist evaluated at NIRS with phase I-II studies [16]. A phase III study that assess the benefit of CIRT is ongoing at HIT (HIT-1) [17]. We investigated SBCSC due to their interesting pattern of relapse.

In-field LRF remains the most common type of failure. Marginal LRF arise adjacent to the original tumour volume but immediately outside the primary treatment target volume where a dose reduction is imposed by the proximity of organs at risk [18-21]. This concept will be clearly defined later. Maximum diameter, regional invasion, volume of the GTV, tumour dose and homogeneity, location of the tumour and age appeared as prognostic indicators of local control [15, 21].
On the other hand atypical recurrences – i.e. out-of-irradiation field such as surgical pathway, nodal, intradural – are however reported by numerous oncologists [22]. Their analysis may help the physician to better understand the definition of the target volumes and their coverage with the appropriate dose level.

A retrospective study was performed on 371 patients treated at the Institut Curie-Orsay Protontherapy Center between 1995 and 2009. With a median follow-up of 27 months (13-96), 13 patients developed an atypical LRF (G.Vogin et al., submitted). Table 1 and Figure 2 summarize the initial presentation and treatment on the one hand and the relapse modality and its management on the other hand.
Table 1: Description and management of the 13 patients who experienced atypical relapse.
Figure 2: Illustration of the atypical relapses encountered in our series. **Top Left:** Patient #2: latero vertebral (short thin arrow) and sub cutaneous left cervical relapses (long thin arrows) under the stable primary cervical chordoma (large arrow; coronal T2 weighted fat saturated MR image). **Top Right:** Patient #2: synchronous sub cutaneous metastasis of the skull; (axial FLAIR MR Image). **Center Left:** Patient #12. Left panel: prevertebral drop cells (thin arrows) issuing from the primary cervico clival location (large arrow), sagittal T2 weighted MR image. **Center Right:** Patient #8: Secondary tumour of the philtrum (thin arrow) on the surgical pathway, 13 months after a rhino septal approach for a clival chordoma (large arrow); (sagittal gadolinium enhanced T1 weighted MR image). **Bottom Left:** Patient #1: temporal bony relapse (thin arrow) on the surgical pathway, 26 months after the first surgery, (Axial gadolinium enhanced fat saturated T1 weighted MR image). **Bottom Right:** Patient #3: Naso septal relapse 96 months after the surgery. The tumour is located on the biopsy pathway (large arrow) (coronal gadolinium enhanced T1 weighted MR image)
Figure 3: Second RT course in patient #1, exclusively reirradiated by one proton beam. Isogray™ (Dosisoft) treatment planning system. **Top:** November 2008: 74.0 Gy (RBE) delivered on the HR-PTV1 (pink shaded area) for a clival chordoma. **Bottom:** January 2010: 64.8 Gy (RBE) delivered on the HR-PTV2 (red shaded area) for the pterionic recurrence (protons only). **Center:** Cumulative planning. Note that the left optic nerve received less than 55.0 Gy (RBE).
Matched CT scan and MR imaging were used to delineate target volumes (detailed elsewhere [23]) Biopsy or surgical pathways were usually not entirely included into the CTV.

Three dose-regimens were successively used. From 1994 to 2000, 64 patients were enrolled to receive 67 Gy (RBE) (45 Gy by photons and 22 Gy (RBE) by protons) [21] and from 2001 to 2005, 198 patients received 71 Gy (RBE) (45 Gy by photons and 26 Gy (RBE) by protons) [24]. Since 2006 dose may be escalated up to 74.0 Gy (RBE) depending on the homogeneity of the dose covering the high-risk volume and the OAR constraints (n=107) [23]. For protons a generic RBE of 1.1 was applied as recommended by the ICRU-IAEA [ICRU 2007].

Consideration might be given in regard of the inclusion of operative routes in the postoperative irradiation fields; e.g. for selected patients with adverse prognostic factors after multiple surgeries in a long time interval [25]. However in such situations, a substantial volume of healthy tissues will be irradiated and may suffer from adverse reactions - that must be balanced against the scarcity of these relapses.

Protons are generally used as a re-irradiation procedure due to the sharper ballistics they offer.

Carbon ion RT is an option thanks to the biological enhanced efficiency. A reirradiation study with CIRT is reported by S.Combs et al. Local tumour control after re-irradiation was 92% at 24 months and 64% at 36 months [26].

The same classification of tumour relapse could be applied to tumours treated with CIRT using an appropriate CRF (appendix)

4. METHODOLOGY PROPOSED FOR ASSESSING OUTCOME AND PATTERNS OF RELAPSE IN CIRT AND LITERATURE REVIEW

Locoregional failure (LRF) remains the predominant pattern of failure in tumours treated with high-precision RT, and especially particle RT, with the majority occurring "in-field" within the high-dose volume.[27] Marginal failures can occur, particularly in the vicinity of the spared OAR. The therapeutic index of high-precision conformal RT is largely dependent on adequate selection and delineation of target volumes and organs at risk. In that aim multimodality imaging fusion with planning CT offers a gain in accuracy. The practical use of functional/molecular imaging in RT optimization must take into cautious consideration several factors whose influences are still not clearly quantified or well understood including (1) patient positioning differences between the planning computed tomography and functional/molecular imaging sessions, (2) image reconstruction parameters and techniques, (3) image registration, (4) target/normal organ functional segmentation, (5) the relationship governing the dose escalation/sparing warranted by the functional/molecular image intensity map, and (6) RT-induced changes in the image intensity map over the course of treatment.

Here we propose a method based on 3 state-of-art photon RT approaches and multimodality imaging to assess the pattern of relapse/severe toxicity applicable to CIRT.

4.1. APPROACH 1: Real vs. planned dose delivery ⇒ Did the target volumes and OAR receive the proper planned dose during RT?

During primary (CI)RT course: treatment-day dose evaluation may be performed to assess how the planned dose differed from the really delivered dose. Anatomical changes (e.g. tumour shrinkage, radiation-induced oedema, or weight loss) may indeed impact dose coverage of the target.

4.1.1. 3D percent dose difference map (dose difference maximal intensity projection, Siemens™).

Megavoltage cone-beam CT images acquired on the treatment day are used for generating the dose difference index. Each index is represented by different colours for underdose, acceptable, and overdose regions. A maximal intensity projection (MIP) algorithm is developed to compress all the information of an arbitrary 3D dose difference index into a 2D DD-MIP image. In such an algorithm, a distance transformation is generated based on the planning CT. Then, two new volumes representing the overdose and underdose regions of the dose difference index are encoded with the distance transformation map. The distance-encoded
indices of each volume are normalized using the skin distance obtained on the planning CT. After that, two MIPs are generated based on the underdose and overdose volumes with green-to-blue and green-to-red lookup tables, respectively. Finally, the two MIPs are merged with an appropriate transparency level and rendered in planning CT images.

**Figure 4:** The MIPs (left) and PDoseDiff maps (right) in the 6th and 21st fractions. There are obvious dose differences (red areas) in the Fx21.[28]

### 4.1.2. Dose guided RT (DGRT)

Daily or weekly three-dimensional images of patients in treatment position are acquired for image-guided radiation therapy. These images can be used for calculating the actual dose delivered to the patient during treatment after corrections (cupping, missing data artefacts), calibration, completion, recontouring, and dose recalculation.

**Figure 5:** Comparison of the dose different maps on the first week of treatment and the third week overlaid on the planning kVCT image. The colours are windowed to show PDDiffs of greater than 5% (red), less than –5% (blue), and within 5% (green); [29]
4.2. APPROACH 2: Visualize the relapse ⇒ when and where did the relapse/harm take place?

4.2.1. Multimodality imaging, a way to approach tumour metabolism and heterogeneity within a rather homogenous morphology

In RT, staging, treatment planning, monitoring and evaluation of response are traditionally based on computed tomography (CT) and magnetic resonance imaging (MRI). These radiological investigations have the significant advantage to show the anatomy with a high resolution, being also called anatomical imaging. In recent years, so called biological imaging methods which visualize metabolic pathways have been developed. These methods offer complementary imaging of various aspects of tumour biology. To date, the most prominent biological imaging system in use is functional MRI and positron emission tomography (PET), whose diagnostic properties have clinically been evaluated for years.

Subsets of tumour cells within the GTV may be more resistant to RT due to adverse biological factors [30]. PET brings in the crucial functional and molecular information, which enable the direct evaluation of tumour metabolism, cell proliferation, apoptosis, hypoxia and angiogenesis according to the PET tracer used [31]. Complementarily, MRI allows the determination of parameters distinctive of tumour tissue as hydrogen-ion concentration (pH) and vessel characteristics as angiographic structure, hemodynamic, vessel permeability, and vessels size. [Ostergaard, 1996 #128; Tropres, 2004 #129]

The Standardized Uptake Value (SUV) is often used in PET imaging for (semi-)quantitative analysis, calculated either pixel-wise or over a region of interest for each image of a dynamic series according to time, ratio of tissue radioactivity concentration, injected dose and body weight.

The term “biological target volume” (BTV) is aimed at defining biologically interesting sub-volumes (field in field) of the tumour like a target within the GTV, which could be irradiated with a higher dose [32]. The goal would typically be identification of the entire tumour with an optimal match between the size of the BTV with the true tumour size and metabolism at histology.

However PET images must not be used solely to delineate volumes due to their low spatial resolution, enhanced by organ motion, and high-noise characteristics [33].

PET gives quantitative information on relative tracer uptake – that is usually manually processed, thus subject to high variability between operators. A single SUV cut-off is unlikely to be adequate to define tumour edges due to inter individual normal SUV variation based on patient body habitus. “Intelligent contouring” was developed by one group [34].

Although available radiotracers have exquisite specificity for a biological process, non specific uptake has been seen with virtually all PET tracers (post RT tumour infiltration by macrophages, active infections, inflammation, recovery…)

4.2.2. Multimodality imaging and subGTV delineation: contribution in different endpoints

The critical influence of tumour volume on treatment outcome in several cancer locations is well established. Early response assessment during the treatment course, while adjustments in therapy can still be made, has been a challenge because of the difficulty in accurately measuring tumour volume, irregular shapes and non-linear tumour shrinkage during treatment.

Tumour response assessment with multimodality imaging can be appreciated at different time points.

- Multimodality imaging prior RT: contribution in generating initial RT plan

PET helps the oncologist to guide volume delineation based on biological processes and dose prescription. 18F- fluorodeoxyglucose (FDG) PET imaging is used in a wide variety of malignant tumours with sensitivities, specificities and accuracy often in the high 90th percentile range. Pre-RT FDG-PET uptake may be a surrogate for proliferation or hypoxia in head and neck patients [35]. GTV definition with PET/CT fusion has been clinically implemented after state-of-art prospective studies mainly in NSCLC, H&N, GBM and Hodgkin lymphomas [36, 37][38].
An attempt to associate imaging findings and pathology was recently performed in 34 patients with NSCLC underwent CT and FDG-PET before lobectomy. Specimens were examined microscopically for microscopic extension. The gross tumour volume (GTV) on CT and PET (GTV\text{CT} and GTV\text{PET}, respectively) was compared with the GTV and the CTV at pathologic examination. Both CT and FDG-PET accurately visualized the CTV(path) in low-risk tumours but underestimate it in high-risk tumours [39].

Other radiotracers are assessed in glioblastoma delineation such as \text{11C}-methionine and O-(2-\text{[18F]}fluoroethyl)-l-tyrosine (FET); their relative uptake is correlated with tumour control [40, 41].

- Multimodality imaging during RT: contribution to modify the RT course

Tumour regression or metabolic modifications under RT have been correlated with local response in several situations. MRI-based 4-dimensional volumetric tumour regression pattern during ongoing cervical RT was recently found to correlate with RT responsiveness. Serial 3-dimensional volumetric MRIs were performed before RT, at 20 Gy, at 50 Gy and at 1–2 months post RT in 115 patients with a mean follow up of 5.3 years. The temporal threshold criteria of proportional tumour at 45–50 Gy and 1–2 months post-RT independently correlate with local control and survival and can lead to treatment adaptation [42].

Changes in the Brownian motion of water within tumour tissue as quantified by using diffusion imaging could also be used as a biomarker for early prediction of treatment response in brain tumours [43].

- Multimodality imaging before vs. after RT: predictive imaging biomarker

FDG-PET in Hodgkin lymphoma is implemented in daily practice to stratify treatment intensity [37]. The relative uptake measured after initial chemotherapy can guide the need for additional RT. The relative tracer uptake assessed prior and after RT may correlate with local control.

Ten patients with LRF of non-small cell lung cancer (NSCLC) underwent FDG-PET/CT before, during, and in the 4–12 months following curative chemoRT using a combined PET/CT scanner. PET-revealed partial in eight patients and complete metabolic response in two patients during RT. Six to nine months after RT, LRF was diagnosed in all patients with both methods. Tumour recurrences were localized mostly in the most active subvolumes of pre-therapeutically metabolic regions of the primary tumour [44].

PET responses were prospectively assessed among 88 patients after concurrent platinum-based radical chemo/RT for NSCLC. Metabolic imaging was acquired prior RT and at a median of 70 days after RT. Complete metabolic response warranted a better LC (p = 0.009) [45].

4.2.3. Multimodality imaging and functional sub OAR delineation

RT-induced injury can be apprehended by anatomical (structural) changes in affected organs or functional, molecular and cellular processes. RT first commonly causes changes that can be detected by planar X-ray or CT imaging. For example, in patients treated for lung or breast cancer, approximately 50–100% and 0–63%, respectively, have radiologic evidence of lung damage via chest X-ray or CT.[46]

These changes in imaging, however, do not necessarily correlate well with symptomatic injury. On the other hand, the potential advantage of functional and molecular imaging over anatomic imaging is that it may be more physiologically and clinically important, and may better reflect underlying pathophysiologic processes.

Data for several organ systems such as lung [47], heart [48], liver [49], brain [50] and parotid [51] have already revealed correlations of radiation dose with changes measurable by a variety of functional imaging modalities.

It appears possible to delineate sub compartments of OAR using multimodality imaging raising the possibility to spare not only full-OAR integrity but also sub-OAR function. RT of cephalic tumours is limited by the differential sensitivity of CNS normal structures. In CNS, specific functions are ensured by sub compartments with specific molecular and cellular architecture [52]. Fiber tract trajectories in coherently organized brain white matter pathways can be computed from in vivo diffusion tensor magnetic resonance imaging giving insight on brain fibers pathways [53].
4.2.4. SubOAR delineation: correlation with improved tolerance?

Multimodality imaging first helps the radiation oncologist to better delineate the target volumes and thus indirectly spare more healthy tissues leading to a better tolerance. In pharyngo-laryngeal squamous cell carcinoma, target volumes delineation based on pre-treatment FDG-PET spares significantly more irradiated volume compared to pre-treatment CT-based delineation. Pre-treatment MRI-based GTV delineation offers moreover a supplemental reduction in the irradiated volumes. However, automatic delineation of FDG-PET GTV could not be performed during RT due to peri-tumoral inflammation.[54]

Multimodality imaging can be directly used to predict RT-induced toxicity. A relationship between FDG uptake in pulmonary tissue after radical RT and the presence and severity of radiation pneumonitis was recently evidenced in NSCLC. (18)F-FDG-PET was performed at a median of 70 days after completion of RT in 88 patients who received 60 Gy in 30 fractions + platinum-based chemotherapy. There was a significant association between the worst RTOG pneumonitis grade occurring at any time after RT and the PET radiotoxicity grade (one-sided p = 0.033) [55].

Single photon emission computed tomography (SPECT) provides a map of the spatial distribution of lung perfusion and can be used to divert dose away from higher-functioning lung, potentially reducing lung toxicity in thoracic irradiation. In 5 patients treated with IMRT on thoracic tumours, healthy lung was segmented into four regions on the basis of SPECT intensity in the SPECT plan. During treatment optimization, dose was sequentially allowed to the target via regions of increasing SPECT intensity. This process results in reduction of dose to functional lung, reflected in the dose-function histogram (DFH). In all patients, DFHs of the two highest-functioning SPECT regions were reduced, whereas DFHs of the two lower-functioning regions were increased [56].

4.2.5. The question of timing

Optimal planning of imaging follow-up is debatable and depends on tumour site and aggressiveness. We must weigh the risk of not detecting early recurrence accessible to a safe and curative local treatment against the risk of excessive repetition of invasive irradiating and expensive investigations. Thoughts were given by ESTRO in NSCLC [57].

A close collaboration with radiologists and nuclear physicians is highly recommended.

4.3. APPROACH 3: Correlate with a given dose level ⇒ which part of the target volume/OAR is involved?

4.3.1. The concept of in-field, marginal and out-of-field failure

Prospective series have demonstrated patterns of failure after RT in H&N, NSCLC, GBM [27, 58, 59]. Imaging that documented failure after RT were usually fused to the original treatment plans for recontour and dosimetry analysis in the most recent studies. The aim is to link low dose regions to the subsequent areas of failure. The method of characterizing failures as in-field, marginal, or out-of-field was described elsewhere [60].

Briefly a relapse target volume (RTV) was identified on the post treatment CT, PET/CT, or MRI. RTV was then mapped to the planning CT scan to determine its isodose line (IDL) coverage. “In-field” failures were defined as having a RTV≥95% within the 95% IDL. “Marginal” failures had a RTV 20-95% within the 95% IDL. “Out-of-field” failures had a RTV<20% inside the 95% IDL.

In case of in field or marginal failure the dose variation within the volume of interest compared to initial planning can be performed using the cumulative dose-corrected CT thereafter calculated.

Precise analysis of treatment failure can lead to novel recommendations on CTVs delineation as it has been done in rectal cancer.[61]

4.3.2. Contribution of multimodal imaging

The BTV concept should also be helpful in assessing the biological response of tumour to RT particularly interesting in locating a LRF according to pre-RT GTV and BTV. Inadequate BTV coverage is supposed to be associated with increased risk of LRF.
The relapse GTV/BTV can be setup on the planning CT. Pre-treatment and failure imaging scans can be registered to determine if the exact anatomical site of LRF coincides with the pre-treatment PET in defined tumour sites. In a recent study performed in H&N, pre-treatment and failure imaging scans were registered to determine if the exact anatomical site of LRF coincides with the pre-treatment PET defined GTV. All except one LRF occurred in the pre-treatment PET-BTV [62]. The same methods was performed in high-grade glioma based on $^{18}$F-FET [63] and $^{11}$C-methionine [40] PET planning prior and after chemo- and RT. Although most of LRF occurred in-field (within PTV), the degree of GTV and BTV mismatch correlated with local outcome was significant only in the second study.

4.3.3. Tumour heterogeneity and dose painting

Theragnostic imaging for radiation oncology is the use of molecular and functional imaging to prescribe the distribution of RT in four dimensions — the three dimensions of space plus time — of RT alone or combined with other treatment modalities in an individual patient. It aims to map the distribution of a tumour, tissue, or functional feature, and to provide information about the clinical response of tumours or healthy tissues to RT. Dose-painting was the term coined to visualize tumour sub volumes (i.e. BTV) with a potential resistance problem and to paint some additional dose onto that volume [32]. This notion was applied in a study by Chao et al. who identified regions with pronounced retention of $^{60}$Cu-ATSM on a PET scan of a patient with H&N squamous-cell carcinoma [64].

In a planning study, they showed that 80 Gy could be delivered in 35 fractions to the hypoxic compartment of the GTV, with 70 Gy in 35 fractions delivered to the rest of the GTV. By use of standard bioeffect modelling to adjust for the slightly higher dose per fraction in the hypoxic target volume, the EQD2 to this volume is about 82 Gy. The researchers used DVH to show that this dose distribution could be planned and delivered by means of inverse planned IMRT.

Dose-painting by numbers is a strategy by which the dose distribution delivered by inverse planned IMRT is prescribed in four dimensions. Painting by numbers introduces gradients of biological function or three-dimensional distributions of the density of radioresistant cellular phenotypes vs. the binary information with lower resolution given by PET (up taken voxels are either inside or outside the BTV) [65].

A hugely challenging, topic of research is to establish the prescription function that is the mathematical link between a specific value of an imaging variable and the optimum clinical dose to be prescribed to the corresponding voxel.

4.3.4. The same approach may be used to assess late (severe) toxicity

Except in the lung, radiation harm is hardly viewable on CT imaging. Multimodality imaging in parenchyma and endoscopy in cavities are prerequisites to precisely graduate toxicity and recontour the wound on the planning CT. Correlations between wound location and measures derived from treatment planning have to be evidenced in order to link high dose region(s) to the subsequent areas of morbidity as it was performed in the previously reported brachytherapy experience [6].

Using data from the RT01 prostate RT trial, the dose to the rectal wall was projected on a two-dimensional map. In order to characterize the dose distribution, its centre of mass, longitudinal and lateral extent, and eccentricity were calculated at different dose levels. Furthermore, the dose-surface histogram (DSH) was determined. Rectal bleeding was most strongly correlated with the lateral extent of the dose distribution. For loose stools, the strongest correlations were found for longitudinal extent; proctitis was most strongly correlated with DSH [66].
4.4. CIRT specificities

4.4.1. In vivo PET imaging

In vivo PET imaging uses the beta emitting properties of carbon ion fragments. $^{10}$C and $^{11}$C isotopes stop at the same location as the native beam and annihilate. As beta emitters, they generate two synchronous gamma rays in opposite directions that may be detected with a dedicated in situ PET camera (short lifespan of the fragments). By correlating the measured activity with the planned treatment and the actual patient anatomy as given by a computed tomogram, it is possible to infer valuable information on the actual dose delivery. The accuracy may reach up to 2 mm without overexposure. PET-based verification might be beneficial for patients having metallic implants, where known shortcomings of the treatment planning algorithms in combination with artefacts of the CT-based patient model are of major dosimetric concern in ion beam therapy [67]. Such monitoring will be implemented at HIT during a pilot study on 240 patients who suffer from tumours of the brain, skull base, head and neck region, upper gastrointestinal tract including the liver, lower gastrointestinal tract, prostate and pelvic region: the MIRANDA study [1].

4.4.2. Tumour heterogeneities, dose painting and the RBE issue

CIRT is aimed to treat localized, bulky, not operable, radioresistant/hypoxic tumours with complex anatomical topography, where the target and the OAR are in direct proximity. Local/regional control is the priority. There is an increased heterogeneity in large tumours with the presence of cells of increased radioresistance, hypoxic state, and proliferation ability. CIRT ensures a better dose distribution and target coverage is feasible due to the Bragg peak and a reduced penumbra. Furthermore, critical structures surrounding the tumour can be completely spared reducing the risk of both acute and late normal tissue toxicities and increasing patient quality of life [68].
CIRT and especially active scanning delivery is able to irradiate a given target volume with a voluntarily heterogeneous dose profile guided by tumour/OAR metabolism and thereby boost the dose to radioresistant subvolumes based on non-invasive functional imaging (dose and LET painting) [69].

There is an initial increase in the relative biological effectiveness (RBE) with the LET. Radiation response to high-LET -compared to low LET- radiation is less influenced by hypoxia, position in the cell cycle and DNA repair capacity as observed in such radioresistant subvolumes [70, 71].

However CIRT precision may decrease due to Bragg peak degradation as a result of heterogeneities in interposed tissues [72].

On the other hand CIRT delivery is likely to generate unexpected heterogeneities especially again in spot scanning due to the interplay effect (cf. JRA-WP2.5) [73]. This occurs as organ movement has to be synchronised with the scanning, increasing the risk of a geographical miss of the tumour that may be a particular issue for health tissues due to the increased RBE of the particles. Additional parameters may affect the range and the dose delivered to the interest voxels: tumour shrinkage, weight loss… Position error was found to be time dependent and this was amplified in the secondary scanning direction causing more dose heterogeneity [74].

4.5. Minimal data set recommended

To adapt the previous methodology to relapse studies in CIRT, the following dataset has to be collected. The initial morphologic imaging that gives insights in GTV volume, morphologic heterogeneity and anatomical relation. In addition to CT, MRI may be useful in various tumour sites such as pelvic, cephalic and limb tumours The initial PET imaging gives additional data about the biological heterogeneity leading on the delineation of the BTV in non operated tumors. It is the responsibility of the radiation-oncologist in charge to combine the information provided by a careful clinical examination and the different diagnostic approaches (e.g., multimodality imaging) and as a result to delineate the CTVs, PTVs, and OAR. Treatment planning system then may merge these data, and optimizes the RT course. On the other hand the applied RBE values and resulting equieffect dose distributions depend on the selection of the radiobiological models and the numerical values of the included parameters. However we recommend to preserve the physical dose map. Periodic control imaging (kV, MV, CBCT, in vivo PET) have to be stored to evaluate the real-time anatomy modification and related dose delivery and identify deviations during RT. They permit an adaptive RT delivery. Evaluation imaging whatever their nature and timing will visualize treatment failure and toxicity during the follow-up. They may be merged with the initial CT planning and support relapse contouring and dose recalculation.

4.6. Summary:

<table>
<thead>
<tr>
<th>Approach</th>
<th>Aim</th>
<th>Tool(s)</th>
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<tbody>
<tr>
<td>Approach 1</td>
<td>Dose recalculation ⇒ Did the target volumes or OAR receive the proper planned dose during RT?</td>
<td>3D percent dose difference map with regular IGRT images[29], in vivo PET[75], back to physical dose map</td>
</tr>
<tr>
<td>Approach 2</td>
<td>Relapse kinetics ⇒ When and where did the relapse/toxicity take place?</td>
<td>Periodic multimodal imaging (x months)</td>
</tr>
<tr>
<td>Approach 3</td>
<td>Dose/volume correlation ⇒ Which part of the target volume/OAR is involved?</td>
<td>Fusion, corrected DVH, recontouring, dose recalculation</td>
</tr>
</tbody>
</table>
5. CONCLUSION

3D Dose–outcome relations could be developed based on long-term patient follow-up studies such as a retrospective matched pair analysis or within a prospective study.

Matching criteria are dependent on the investigated tumour site but may be: age, tumour location, histology, maximum diameter, volume of the GTV, dose.
REFERENCES


APPENDIX

In the following material an exemplary CRF for outcome analysis is presented. This CRF has to be adapted according to the specific needs of the investigated tumour site. In general, target volume definitions and DVH analysis should follow the principles as explained in previous work packages. However, assessment of subvolumes of the tumour/target volumes (e.g. high risk CTV, low risk CTV) as well as definition of specific dose parameters may be reasonable in selected tumour sites.

EXEMPLARY CRF FOR OUTCOME ASSESSMENT
IN CIRT

Study name/acronym
CIRT center
TPS; version

Patient
Initial performance status (ECOG 0/1/2/3/4)
Weight (kg)
Initial symptoms

Tumor assessment

tumor location and extension
prior-RT GTV volume
prior-RT GTV largest dimension
imaging modalities
- PET (radiotracer) (FDG, MISO, 5-FP....) area of uptake, SUV max
description of BTV if relevant
- MRI
- CT-scan

Previous treatment of the present tumour
• Chemotherapy (number of cycles)
• Surgery: number of surgeries, time between first and last surgery, pathways, margins quality
• RT: date, dose, fractionation, technique, balistics, DVH, tolerance

Planned RT course

Modalities
- definitive particle therapy
- combined modalities

Prescribed dose

<table>
<thead>
<tr>
<th>Target volume</th>
<th>Prescribed dose (Gy)</th>
<th>technique</th>
<th>Fractionation</th>
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<td>If combined photon technique, precise</td>
<td>Dose per fraction (Gy)</td>
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Example for possible high risk and low risk CTV definition in CIRT for skull base chordoma:

GTV is the visible residual tumor on the pre-radiotherapy CT and/or MRI scan.

HR-CTV includes the surgical bed around the residual GTV (R2 surgery in most cases) defined according to the pre-operative CT and/or MRI scan

LR-CTV includes:
- The HR-CTV + 5 mm isotropic expansion, excluding anatomical barriers (uninvaded neurological or bone structures)
- The whole clivus
- The two cavernous sinuses
- When first trans-sphenoidal and/or the HR-CTV includes the sphenoid sinus in part: all the walls of the sphenoid sinus
- For other anterior approaches: the mucosa of the posterior pharyngeal wall next to the HR-CTV (included within automatic expansion around the GTV in most cases)
- Fat filling in the tumor bed (fat beyond is not included in the CTV-BR)

### Treatment planning data

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<tr>
<th>Target volume</th>
<th>Volume (mL)</th>
<th>Absorbed Dose ICRU point</th>
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<th>D_{\text{relative}} (e.g. 50%)</th>
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<th>D_{\text{relative}} (e.g. 2%)</th>
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<th>D_{\text{absolute}} (e.g. 0.1cc)</th>
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Margin from CTV to PTV (mm) – one line for each technique (if not protocolar)

Margin from OAR to PRV (mm) – one line for each technique (if not protocolar)

Interruption?
Q/A and dose-corrected RT course

control imaging (kV, MV, CBCT, PET)

treatment planning deviations:
* day/week1 ...... corrections that were done (should have been done): x1, y1, z1
* day/week2...... corrections that were done (should have been done): x2, y2, z2
etc

Corrected Treatment data

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Radiobiological model to calculate bioeffective dose from absorbed dose:
Tumor Control/toxicity

one page /M2, M4, M6...... M24

- Performance status (ECOG 0/1/2/3/4)
- Weight (kg)
- Symptoms

Evaluation imaging modality
- PET (radiotracer) (FDG, MISO, 5-FP....) area of uptake, SUV max, extension
- MRI
- CT-scan

GTV largest dimension

GTV volume
- Complete response
- Partial response
- Stable disease
- Progressive disease

Tumor recurrence
- in radiation field
  - central within GTV
  - marginal within CTV (high risk, low risk etc.)
- out of radiation field
- distant

Relapse GTV delineation and superimposition on planning CT:
- volume of relapse GTV ∩ initial GTV
- volume of relapse GTV ∩ initial CTV
- volume of relapse GTV ∩ initial PTV

QOL (6, 18 month, end of study visit)

Adverse events/complications since last visit (CTACEv4.0)

Injured OAR delineation and superimposition on planning CT (if visible)
- volume of injured OAR ∩ initial OAR
- volume of injured OAR ∩ initial PRV