Imaging and high-dose proton therapy in chordomas and chondrosarcomas of the axial skeleton

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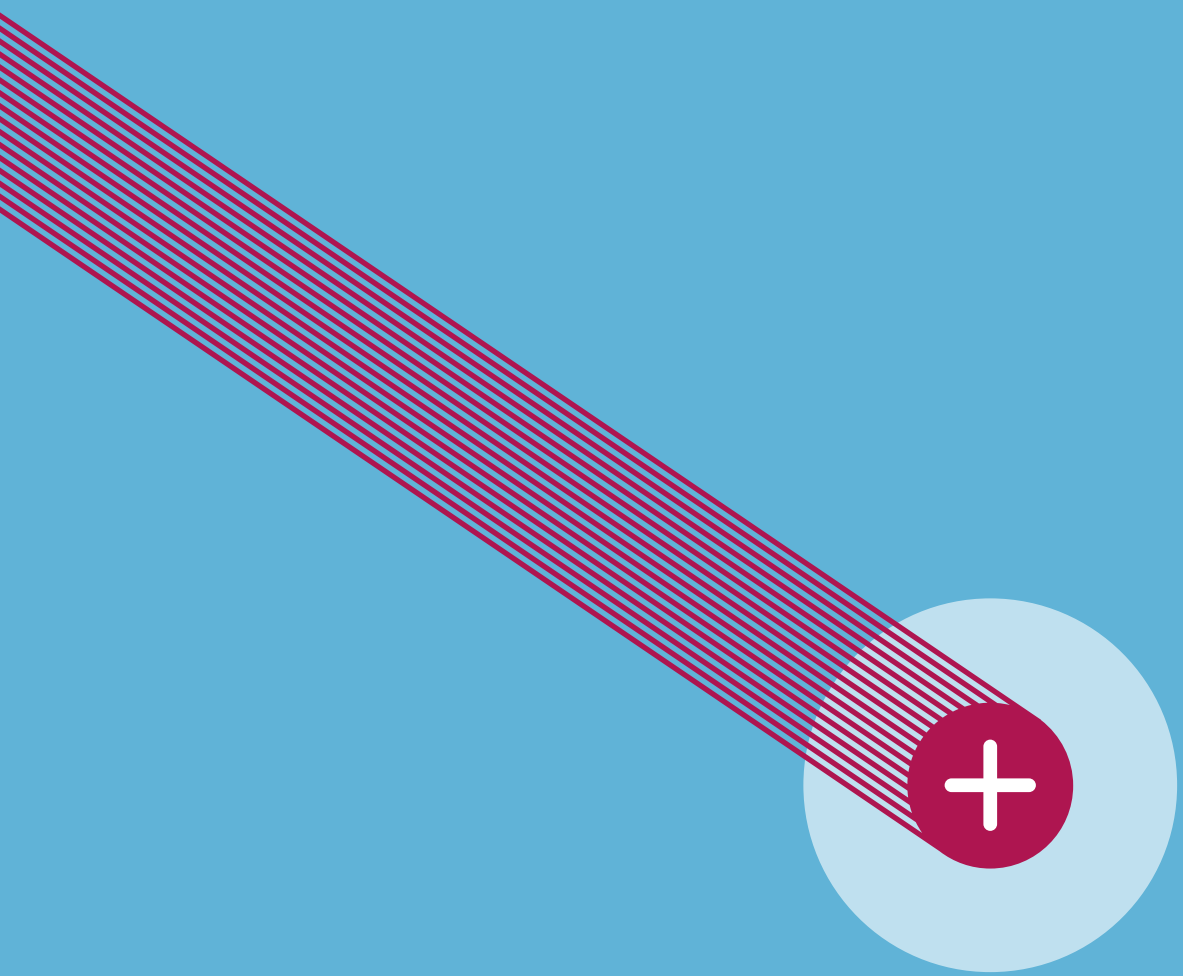
CHAPTER 8

Summary and General discussion
Samenvatting en algemene discussie



8.1 Summary

Chapter 1 provides a general introduction to the thesis. The primary objective of this thesis is to identify a set of functional MRI parameters that portray early changes occurring within the chordomas and chondrosarcomas located in the axial skeleton, during, and respectively 6 months and 1 year following proton therapy. Secondary objectives are to determine imaging parameters that can portray proton therapy-induced changes; which imaging parameters and sequences are most useful in differential diagnosis of chordomas and chondrosarcomas; and optimization of intensity modulated proton therapy. The final objective is to describe clinical and imaging outcomes and identify side effects in the first cohort of chordoma and chondrosarcoma patients treated with proton therapy at HollandPTC, the proton therapy center in Delft, The Netherlands, founded by Erasmus MC, LUMC and TU Delft.

Application of morphological MRI and CT features in combination with functional MRI parameters for diagnosis of primary bone tumors in the axial skeleton is presented in Chapter 2. Morphological and functional MRI parameters of pre-treatment MRIs of 80 patients with a histological diagnosis of a primary bone tumor of the axial skeleton were retrospectively analyzed. Functional parameters were measured in 4 circular regions of interest per tumor placed on non-adjacent scan slices. Differences in values of functional parameters between different histologies were analyzed with the Dunn's test. The predominant histology (60.0%) in this cohort of patients was chordoma. Most tumors (80.0%) originated in the midline and had *geographical* (78.2%) bone destruction. *Amorphous*-type calcification (pre-existing bone) was seen only in chordomas. A homogeneous contrast enhancement pattern was seen only in chondrosarcoma and plasmacytoma. *Ktrans* and *Kep* were significantly lower in both chordoma, and chondrosarcoma compared to giant cell tumor of the bone (p=0.006–0.011), and plasmacytoma (p=0.004–0.014). The highest diffusion-weighted MRI (DW-MRI) *apparent diffusion coefficient* (ADC) values corresponded to chondrosarcoma, and these were significantly higher than those of chordoma (p=0.008). Herewith, the most discriminating

morphological and functional MR parameters useful in making a confident diagnosis of primary bone tumors of the axial skeleton were identified.

Chapter 3 addresses the well-known problem of variability and reproducibility of measured ADC values occurring between different institutions and research groups. As ADC is broadly used for differential diagnosis as well as treatment evaluation, variation in values complicates interpretation of results. To determine the impact of acquisition and post-processing methodologies on measured ADC values three commonly used DW-MRI sequences with three randomly selected commercially available software packages were tested. For this purpose, chest and pelvic areas of four healthy volunteers were scanned on a 3.0T scanner with three diffusion-weighted MRI sequences: inversion-recovery spin echo echo-planar imaging (IR-SE-EPI), turbo spin echo SPectral Attenuated Inversion Recovery (TSE-SPAIR) and TSE without fat suppression. ADC values for each sequence were measured in ten different circular regions of interest within the muscle tissue of each volunteer using the following software packages: IntelliSpace Portal (ISP) (Basic diffusion package, version 10.1, Philips, Best, The Nether-lands), IDS7 - Picture Archiving and Communication System (PACS) (Sectra Workstation IDS7, version 23.1, Linköping, Sweden) and RayStation (RS) (version 10B, RaySearch Laboratories, Stockholm, Sweden). Mean ADC, standard deviation (SD), and variation coefficients (VC) were determined. Differences in ADC mean ranks between different DW-MRI sequences and different software packages were analyzed with the Kruskal-Wallis and post hoc Dunn tests. Results showed that mean ADC values varied from $0.610 \cdot 10^{-3} mm^2/s$ to $2.537 \cdot 10^{-3} mm^2/s$. Ranges of SD and VC were $0.163 \cdot 10^{-3} mm^2/s$ – $0.456 \cdot 10^{-3} mm^2/s$ and 10.0% – 52.6%, respectively. Mean ranks of ADC obtained with TSE without fat suppression sequence were significantly different to those of IR-SE-EPI ($p=0.001$) and TSE-SPAIR sequences ($p=0.0004$). The IR-SE-EPI sequence had the lowest variation coefficients of 10.0%, 16.6% and 19.5% when measured with RS, PACS and ISP, respectively. From these results it can be concluded that although ADC values vary with acquisition and post processing methods, the IR-SE-EPI sequence is the most stable across different software packages. Discrepancies in ADC measurements between different institutions and research groups could be minimized when using the IR-SE-EPI sequences.

The comparison between software packages remains challenging however, due to the large number of packages available and their constant updates and upgrades.

The clinical experience with robustly optimized intensity modulated proton therapy (IMPT) and treatment related toxicities in the first skull base chordoma and chondrosarcoma patients treated with proton therapy at HollandPTC, Delft, The Netherlands are presented in Chapter 4. Clinical data, treatment plans and acute toxicity of patients treated between July 2019 and August 2021 were reviewed. CT and 3.0T MR scans for treatment planning were performed in supine position in a thermoplastic mold. For each patient 21 dose optimization and 28 dose evaluation scenarios were simulated. Acute toxicity was scored on a weekly basis before, during, and at the end of the treatment, as well as 6 months and 1 year thereafter, according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Nine chordoma and 3 chondrosarcoma patients with 1-3 resections prior to IMPT were included; four patients had titanium implants. Brainstem core and surface, spinal cord core and surface were used for nominal plan robust optimization in 11, 10, 8 and 7 patients, respectively. Middle ear inflammation, dry mouth, radiation dermatitis, taste disorder, and/or alopecia of grades 1-3 were noted at the end of treatment in 6 patients without similar complaints at inclusion. These symptoms disappeared 3 months following the treatment. Results of this study show that robustly optimized IMPT is feasible as postoperative treatment for skull base chordoma and chondrosarcoma patients with acceptable early toxicities (grade 1-3), that disappear in the first 3 months following irradiation. In patients requiring stabilization surgery, close collaboration between neurosurgeons and radiation oncologists, before the surgery, on exact placement of implant material and screws is the key for successful irradiation of patients with surgical implants.

Experience with planning and delivery of robustly optimized proton therapy in chordoma and chondrosarcoma of the mobile spine and sacrum is presented in Chapter 5. Robust plan optimization renders the proton beam therapy more predictable upon individual setup errors, however, reports on its application in treatment of chordomas and chondrosarcomas of axial skeleton are, to our knowledge, not available. Therefore, patient,

treatment, and acute toxicity data of all patients with chordoma and chondrosarcoma of the mobile spine and sacrum, treated between April 2019 and April 2020 at HollandPTC (Delft, The Netherlands) were collected and retrospectively reviewed. Anatomical changes during treatment were evaluated by weekly cone-beam CTs (CBCT), supplemented by scheduled control-CTs or ad-hoc control-CTs. Acute toxicity was scored weekly during treatment and at 3 months after therapy according to CTCAE 4.0. Seventeen chordoma and 3 chondrosarcoma patients were included. Coverage of the high dose clinical target volume was 99.8% (range 56.1% – 100%) in the nominal and 80.9% (range 14.3% – 99.6%) in the voxel wise minimum dose distribution. Treatment plan adaptation was needed in 5 out of 22 (22.7%) plans. Reasons for plan adaptation were either reduced tumor coverage or increased dose to the organs at risk (OAR). Results showed that robustly optimized intensity modulated proton beam therapy for chordoma, and chondrosarcoma of the mobile spine is feasible with acceptable toxicity. Plan adaptations due to anatomical changes were required in approximately one out of five treatment courses.

Insufficiency fractures (IFs) occurring in patients with malignancies in the pelvic area who have been treated with radiotherapy are a well-known complication attributed to radiotherapy. Chapter 6 addresses incidence, location, and features of IFs in sacral chordoma patients treated with high-dose radiotherapy and/or resection, relative to radiation therapy type and irradiation plans. Clinical data, including details of all surgical procedures, radiotherapies, and presence of symptoms (pain and/or reduced mobility) of patients histologically diagnosed with sacral chordoma between January 2008 and December 2023 available at Leiden University Medical Center database were retrospectively reviewed. Inclusion criteria were availability of diagnostic- treatment planning- and follow-up imaging (MR and/or CT scans) and, completed treatment. All scans were re-evaluated for presence and location of IFs that were defined as linear abnormalities with/without bone marrow edema (BME)-like changes. Median follow-up time was 49 months (range 3 – 421 months). From 48 included patients (29 male, median age 66, range 27-85), 22 were diagnosed with 56 IFs (45.8%). IFs occurred 3–266 months following the treatment. All sacral and iliac bone IFs had vertical components parallel to SI-joint. Twenty

patients had bilateral and 16 unilateral IFs. BME-like changes were visible in 46 IFs (82.1%, 0.80, p≤0.001). In 13 out of 56 IFs (23.2%) BME-like changes were seen prior to IF diagnosis, in only one patient BME-like changes didn't develop into an IF. Thirty-nine IFs (84.7%) occurred within low-dose radiotherapy volume and 7 IFs (15.3%) were located outside of the irradiated volume in 16 out of 44 irradiated patients. Six IFs occurred in one patient with a chordoma, who was treated with resection only. Four patients with IFs had pain complaints, out of which two required stabilization surgery following which complaints disappeared. In conclusion, pelvic IFs are common in sacral chordoma patients treated with (neo-)adjuvant high-dose radiotherapy and/or resection, occurring months to years following treatment and they do not heal over time. Not all IF occur in the irradiated volume. Although pain may be associated with the primary tumor, and IF can be asymptomatic, the presence of IF should be taken into consideration as a cause of pain. When present, BME-like changes indicate risk of IF developing.

Chapter 7 addresses the prospective study investigating changes of functional MRI and PET-CT parameters occurring during and, 6 months and 1 year following definitive or (neo-)adjuvant high dose proton therapy in sacral chordoma patients. Study inclusion criteria were a histological diagnosis of sacral chordoma, lesion size ≥ 1cm, no MRI contraindication, World Health Organization (WHO) performance score < 3, and definitive 74GyE proton radiotherapy or combined proton radiotherapy (50GyE + resection + 24GyE) at HollandPTC (Delft, Netherlands). The patient inclusion period was between August 2020 and December 2023. The study was approved by the medical ethical committee and all included patients signed the informed consent form. In each patient a 3.0T MRI was made at inclusion, mid-treatment (week 4), end of treatment (week 8), 6 months and 1 year following first fraction. MRI parameters of perfusion, permeability and diffusion were measured with 4 circular regions of interest within the lesion. Two [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography ([^{18}F]FDG-PET) scans were made: prior- and 1 year following first fraction. Standardized uptake value (SUV), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were measured within entire lesion volume after manual segmentation. Temporal changes between imaging timepoints were analyzed with Mann-

Whitney-Wilcoxon test (α=0.05). Ten sacral chordoma patients were included (5 male, 5 female; median age 69, range 39-78) out of which seven received definitive and three (neo-)adjuvant treatment. Perfusion MRI parameters increased already at week 4 and resulted at end of treatment in – Ktrans (-33%, p=0.570) and wash in rate (-47%, p=0.075) compared to baseline. One year following PT SUVmax reduced (-31%, p=0.008). Results of the study show that functional MRI parameters reflect PT-induced changes from week 4 and are characterized by initial increase and later decrease of volume and vascularity. The clinical and [^{18}F]FDG-PET defined treatment outcome was good in all 10 patients.

8.2 General discussion and future perspective

Foci of this thesis are diagnosis, and evaluation of definitive or (neo-)adjuvant high-dose proton therapy combined with surgery of chordomas and chondrosarcomas located in the axial skeleton.

8.2.1 Diagnosis

A correct diagnosis of primary bone tumors based only on morphological features seen on MRI and CT scans is possible in up to 90.0% of the cases when reviewed by two expert radiologists. In a regular clinical setting this percentage probably is lower, as review by a team of two expert radiologists is not a common clinical practice. For optimal diagnostic confidence both MRI and CT scan should be assessed, since important differentiating features such as calcification and bone destruction can be accurately identified only on CT scans, while characteristics of soft tissue components such as pattern of contrast enhancement and cystic areas can only be properly assessed using MRI. Diagnosis based solely on morphological imaging features could be misleading to the specialized, and especially to the general radiologist, as chordomas, chondrosarcomas and other primary bone tumors often present with the same or very similar features. Furthermore, morphological imaging features are relatively prone to subjective interpretation. A good addition to morphological imaging features that can assist in differential diagnosis are

functional MRI parameters, such as perfusion time intensity curves (TICs), and Ktrans and Vp parameters portraying tumor permeability. *Apparent diffusion coefficient* (ADC) values of diffusion-weighted MRI (DW-MRI) proved to be beneficial in differentiating chordomas from chondrosarcomas [1-6 and Chapter 2]. Although MRI and CT may thus be used in contributing to a final diagnosis allowing proper treatment selection, histopathology of a biopsied tumor sample is still required. MRI parameters can also be used to identify the most representative viable parts of the tumor to guide biopsy procedures.

Direct correlation of functional MRI parameters such as Ktrans, Vp, ADC and perfusion TICs with anatomically corresponding histopathology of the tumor specimen would potentially improve the understanding, definitions and thus usefulness of these parameters. Diagnostic biopsy samples of the tumor are often insufficient for obtaining greater certainty of this correlation as only the most active part of the tumor visible on MRI is biopsied, leaving the less active parts of the tumor uninvestigated. This poses a great limitation when studying such heterogenous tumors. Diagnostic imaging including functional MRI, and *en bloc* resection as a definitive treatment would be an ideal setting for this correlation. Despite being the preferable treatment option of chordomas and chondrosarcomas, *en bloc* resection is not always feasible. Joint multicenter and international research studies providing larger cohorts could be a solution by increasing the opportunities to execute these correlations. For the latter special attention should be given to the imaging protocols and postprocessing procedures and software used, as they play an important role in interchangeability of obtained results between different research groups, centers and hospitals [Chapter 3]. Synchronization of protocols and image analysis software is a fairly doable but costly task considering the potential purchase of necessary software licenses. Different models and makes of used scanners can also have an impact on the obtained results. These obstacles can be overcome with ComBat, one of the currently most widely used harmonization techniques. This technique minimizes the setting discrepancies between data batches by transforming them in a such way that they all have the same mean and/or variance [7]. Proper application of ComBat however requires large sample sizes to form the training, validation and testing datasets. Furthermore, in case of different tumor subtypes or potential influence of the anatomical location of the tumor on the measured

values additional covariates accounting for these discrepancies, which further increases the minimum required size of datasets, have to be introduced as well [8].

8.2.2 Monitoring therapy

Aside from their diagnostic potential, functional MRI parameters proved to be a useful tool in assessment of tumor response to radiotherapy by providing an insight into tumor composition, which is a valuable asset in research of radiotherapy-resistant and slow-responding chordomas and chondrosarcomas [9-13]. However, the measured values of these parameters and the changes within the irradiated tumor they are portraying are not fully understood. So far only a handful of articles have reported the benefit of functional MRI parameters Ktrans, Vp and ADC in assessment of chordomas' and chondrosarcomas' response to radiotherapy, yet clear interpretation of these parameters is still lacking [9-11]. In order to better understand the changes occurring within the tumor during and following the treatment, portrayed by these parameters, tidily scheduled imaging examinations and consultations with the treating physician (and other specialists when necessary), are needed to investigate the association of clinical data and functional imaging parameters. Follow-up time should be at least 5 years, as most of the reported progressions and recurrences occur within this time frame regardless of the radiotherapy type (photons or hadrons) [5, 14, 15]. Established associations would facilitate tumor response prediction based on the values of selected parameters measured prior to the treatment and assist in the treatment selection.

In addition to functional MRI, PET-CT also proved to be a good tool in treatment response evaluation, including identification of recurrences and metastasis of chordomas and chondrosarcomas despite their low uptake with the so far used tracers - [^{18}F]-FDG, [^{18}F]-FMISO, [^{68}Ga]-DOTA-TATE, [^{18}F]-FAZA, [^{68}Ga]-FAPI and [^{99m}Tc]-MDP [7, 16-22 and Chapter 7]. A specific chordoma and chondrosarcoma tracer would be beneficial for more detailed and better analysis of their activity. Prospective studies using both PET-CT and MRI at fixed time points are needed to allow a more detailed analysis of both functional MRI and PET-CT parameters. Difficulty of small cohort size was also encountered in the prospective study

presented in this thesis [Chapter 7]. Nevertheless, despite the small cohort size and relatively short follow-up time changes in functional MRI parameters such as Ktrans, Vp, ADC, *time to peak*, *wash in rate* and *wash out rate* were noted already during the first months of treatment. This demonstrates that radiotherapy-induced changes occur as early as 4 weeks following the first fraction. Fluctuations of these parameters during the treatment reflect changes within the tumor in combination with host response in normal surrounding tissue, and host response that extends into the tumor. This complicates, especially in view of limitations in anatomical and time coded histopathological correlation with imaging parameters, a comprehensive understanding modeling of these parameters. Another obstacle, beside the small number of patients, is lack of suitable software for image analysis. Ideal setting for this would be a cohort of patients undergoing (neo-)adjuvant radiotherapy and resection as it was the case with the three patients in the prospective study presented in this thesis [Chapter 7]. This way early changes portrayed by the functional MRI parameters could be correlated with histopathology of the macroscopically resected tumor, as mentioned above in the *Diagnosis* section. Understanding the tumor composition and changes that occur during the treatment would facilitate adjustment of treatment plan and dose regions already during the treatment.

A possible solution for analysis of imaging parameters within the entire tumor volume is the currently emerging imaging analysis method – radiomics. This method comprehends extraction of different imaging features, such as shape, image intensity histogram, relationship between image voxels, etc. from CT, PET-CT scans and T1W and T2W MRI sequences providing an insight into pathophysiological tissue information [23]. Another potential application of radiomics is analysis of spatial patterns on dosimetric maps (dosiomics), which is presumed to be a better approach then dose volume histograms analysis. Yet for the time being radiomics, requiring large datasets, is still far from broad use in chordoma and chondrosarcoma research due to the extremely small cohorts.

8.2.3 Therapy

Despite the positive outcomes of radiotherapy, *en bloc* resection is still the preferable treatment in chordomas and chondrosarcomas, due to the highest local control

rates [24]. However, this evidence is partially biased as resectability of the tumor is highly dependent on its location and extension. As previously mentioned, treatment of tumors located in the spine has a lower morbidity rate than treatment of those located in the sacrum. Furthermore, a large tumor, invading surrounding compartments is a sign of an already advanced disease and is less likely to be fully resected due to related severe morbidity. Therefore, larger tumors are preferably treated with definitive or (neo-)adjuvant radiotherapy combined with more limited resection. This negative selection bias hampers adequate comparisons between the outcome of surgery and radiotherapy as preferred treatment. Whether *en bloc* resection or definitive radiotherapy is a better treatment choice still remains a question. In an attempt to answer this question for sacral chordomas a randomized SACRO trial was set up [25]. However, taking into consideration the rarity of the disease as well as the primacy of patients' choice of treatment over randomization, required cohort size for valid statistical analysis and results is challenging.

Definitive or (neo-)adjuvant high-dose hadrontherapy with limited toxicities has been a successful treatment option for chordomas and chondrosarcomas despite their low sensitivity to radiotherapy [24-26]. Good outcomes with acceptable toxicities were also noted among the first skull base and sacral chordoma and chondrosarcoma patients treated with intensity modulated proton therapy at the HollandPTC in Delft [Chapters 4, 5 and 7]. However, effectiveness of different radiotherapy types, and further improvement of radiotherapy techniques, including the possibility to increase the radiosensitivity of these tumors still need to be investigated. Better local control rates have been reported in patients treated with high-dose hadrontherapy compared to those treated with high-dose photon therapy. This is a direct consequence of the differences in interaction of photons and hadrons with the tumor and surrounding healthy tissue and occurring biological effects. Research results obtained so far, demonstrate that hadrons, especially carbon ions, have greater cell kill capacity in hypoxic, and thus radioresistant tumors like chordomas and chondrosarcomas due to their high linear energy transfer (LET) in the "spread-out" Bragg peak [29]. This resulted in two new ideas of radiotherapy optimization – *LET blocking* where highest LET would be focused on the tumor center and *LET painting* where particles' LET is adapted according to the tumor oxygenation [30, 31].

Another attempt to optimize radiotherapy is hypofractionation where the prescribed high dose is administrated in a smaller number of fractions and correspondingly higher dose per fraction. So far, several studies have demonstrated feasibility of hypofractionated carbon ion therapy with local control rates comparable to regular fractionation [32-34]. First results of randomized phase II clinical trial (NCT01811394) comparing hypofractionated high-dose proton with carbon ion therapy in patients with sacrococcygeal chordoma yielded no significant difference in local control, overall survival or local progression free survival between the two different hadron therapies [35, 36]. Further research on efficacy of hypofractionation is still needed in order to properly asses its benefits over the current fractionation.

Other potential alternative treatment options for chordomas and chondrosarcomas include systemic therapy and hyperthermia. At the moment there are several ongoing phase I and phase II clinical trials investigating vaccines, immune checkpoint inhibitors and other immunotherapies as definitive treatment or combined with radiotherapy [37, 38]. The idea behind the combination of systemic therapy with radiotherapy is to increase tumor radiosensitivity and thus maximize therapy effect or open the possibility to reduce the administrated radiation dose. Results reported so far are promising, with low grade (≤ grade 2) toxicities such as nausea, vomiting, diarrhea, anorexia, etc. [37, 38]. However, a lot about the immune microenvironment of these tumors is still unknown and there is a long way ahead before systemic treatment could become a part of the standard chordoma and chondrosarcoma treatment.

Hyperthermia treatment involves tumor tissue heating to temperatures between 39°C and 42°C. Promising results with improved tumor response reported in cancer patients treated with radiotherapy or chemotherapy and hyperthermia gave an idea of implementation of hyperthermia in chordoma treatment [39]. So far only two studies have reported on its application with proton therapy in patients with sacral chordomas and chordoma cell lines, respectively [40, 41]. The study on cell lines reported significantly lower cell survival in cell lines treated with hyperthermia and proton therapy compared to those treated with proton therapy alone. The study on 10 sacral chordoma patients reported treatment response and toxicity results with an 18-month follow-up period comparable to

previous studies on chordoma patients treated with only proton therapy. Larger patient cohorts and longer follow-up are needed for proper evaluation of the clinical value of hyperthermia as an adjunct to hadrontherapy. The biggest hurdle in implementation of hyperthermia in daily practice its technical complexity and limited availability. In The Netherlands this treatment is not reimbursed by the national health insurance due to the lack of favorable research results supporting its application.

A complicating factor in the interpretation of results of radiotherapy and systemic treatment innovations is, beside the small number of subjects, the use of RECIST and volumetric methods for response evaluation. As previously mentioned, these are not the optimal treatment assessment methods for slow responding tumors. Chordoma, for instance, typically increases in size during the first months following effective proton beam therapy [Chapter 7]. In order to properly assess the tumor response and detect the poor- and good responding areas in these heterogenous tumors, analysis of functional imaging parameters should preferably be performed within the entire tumor volume. Radiotherapy planning software allowing analysis of functional imaging parameters within the irradiated tumor volume during the treatment and treatment follow-up would be an interesting innovation to be tested in the clinical practice of adaptive radiotherapy. Although some of the currently commercially available software allow implementation of image analysis scripts, these scripts still need to be tested on larger cohorts of patients before they can be approved for clinical use.

Regardless of the treatment option chosen (surgery and/or radiotherapy) recent reports on sacral chordoma patients showed evidence of pelvic bone insufficiency fractures occurring as a late post-treatment effect [42-45 and Chapter 6]. The direct cause and the mechanism of development of these fractures are still unknown. However, an already well-known consequence of high-dose radiotherapy is reduction of bone marrow density (BMD) of surrounding healthy bone tissue, previously reported as one of the risk factors for bone insufficiency fractures [46]. Connection between radiotherapy-induced BMD and insufficiency fractures could be investigated by performing dual-energy x-ray absorptiometry (DEXA), known as bone densitometry, prior to the treatment, as a reference, and along the treatment follow-up regardless of patient age, gender and body

mass index (BMI) as these factors are not always related to the incidence of insufficiency fractures [Chapter 6]. Given that median time to diagnosis of insufficiency fractures following treatment is 6 months (range 3 – 266 months), the second DEXA scan should also be performed around 6 – 12 months following the first irradiation fraction. Depending on the result of the follow-up DEXA scan follow-up scanning should be performed according to the guidelines: for DEXA T-score > -1.50 (normal/mild osteopenia), -1.50 – -1.99 (moderate osteopenia) and -2.0 – -2.49 (advanced osteopenia), rescreening interval should be 15, 5 and 1 year, respectively [47]. Furthermore, pre-treatment and follow-up MRI should be made with a more generous field of view (FOV), and not just encompassing the tumor location, especially in patients with sacral tumors. Main motive for larger FOV is the fact that insufficiency fractures can also occur in more distant locations from the low-dose volume where they most often encountered. With low incidence of these tumors and with several, previously mentioned, different treatment options available at the moment, identifying the main cause of occurrence of these fractures will be challenging. However, unlike for functional MRI parameters, synchronization of imaging protocols and creation of a central database among different hospitals and radiotherapy centers across the world, with the aim of obtaining larger cohorts, is more easily manageable. Involvement of administrated high-dose radiotherapy in the incidence and location of insufficiency fractures should further be assessed through radiotherapy plans including dose volume histograms and LET graphs. With high incidence of insufficiency fractures noted within the low-dose volumes more attention should be given to reducing these comprehensive volumes [48, Chapter 6]. This will also benefit further optimization of radiotherapy and potentially help in assessment of effectiveness of hadrons and photons.

In conclusion, research on larger cohorts of chordoma and chondrosarcoma patients with longer follow-up times is needed allowing more advanced statistical analysis that could provide innovative results. Furthermore, correlation of functional MRI parameters and histopathology in larger cohorts would be beneficial for understanding radiotherapy-induced changes occurring within the tumor portrayed by these parameters. With larger cohorts and longer follow-up times a set of functional MRI and PET-CT

parameters predicting clinical outcome such as tumor specific mortality, development of metastases, morbidity secondary to tumor activity and morbidity secondary to treatment could be suggested. This way, based on the changes occurring during the treatment or shortly thereafter, portrayed by the functional imaging parameters, the disease outcome could be estimated, and adequate treatment adaptations could be promptly applied.

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