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Original article

MRI evaluation of sacral chordoma treated with carbon ion radiotherapy alone

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ABSTRACT

Background and purpose: To compare RECIST 1.1 with volume modifications in patients with sacral chordoma not suitable for surgery treated with carbon ions radiotherapy (CIRT) alone. To evaluate patients pain before and after CIRT. To detect if baseline Apparent Diffusion Coefficient values (ADC) from Diffusion Weighted sequences could predict response to treatment.

Material and methods: Patients included had one cycle of CIRT and underwent MRI before and after treatment. For each MRI, lesion maximum diameter and volume were obtained, and ADC values were analyzed within the whole lesion volume. Patients pain was evaluated with Numerical Rating Scale (NRS), considering the upper tumor level at baseline MRIs.

Results: 39 patients were studied (mean follow-up 18 months). Considering RECIST 1.1 there was not a significant reduction in tumor diameters ($p = 0.19$), instead there was a significant reduction in tumor volume ($p < 0.001$), with a significant reduction in pain ($p = 0.021$) if the tumors were above vertebrae S2–S3 at baseline MRIs. The assessment of baseline ADC maps demonstrated higher median values and more negative skewness values in progressive disease (PD) patients versus both partial response (PR) and stable disease (SD).

Conclusions: Lesion volume measurement is more accurate than maximum diameter to better stratify the response of sacral chordoma treated with CIRT. Preliminary results suggest that baseline ADC values could be predictive of response to CIRT.

Chordoma is a rare low-to-intermediate grade bone malignant tumor, which originates from the embryonic notochord's residues within the axial skeleton [1,2]. This disease represents 1–4% of all primary bone tumors, with an incidence of 0.5–0.8/1,000,000 persons per year [3,4]. Most common localization of the disease is the sacrococcygeal region (50–60%), followed by the clival region (25–30%), the cervical region (10%) and the thoracolumbar vertebrae (5%) [5]. En bloc surgery with wide resection margins remains the mainstay treatment. Patients who underwent radical resection show both longer local control and disease-free period compared with subtotal resection. However, sacrectomy with wide margins is very difficult in large chordoma cases, with a high complication rates especially if performed at S2 level or above, and by the time the first symptoms appear, the tumor may be already too large for surgery [1,6–8].

Hadrontherapy is a form of external beam radiotherapy using beams of charged particles, most commonly protons and carbon ions. It is an effective treatment for sacral chordoma, offering a valid alternative for patients not suitable for surgery [9–11]. In the last decades, hadrontherapy aroused a great interest in clinical application because of dosimetric and radiobiological properties of the particles. The common characteristic of both protons and carbon ions is to release low dose of radiation after penetrating the tissue with a steep dose deposition at the end of their range, called Bragg Peak, which is followed by a steep drop, limiting strongly the dose deposition to surrounding healthy tissues [12]. Furthermore,

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carbon ion beams have a higher relative biological effectiveness compared with protons or X-ray beams [13]. Carbon ions produce multiple damages to the DNA reducing the cell intrinsic repair mechanisms. They are been using mainly for radioresistant tumors arising close to organ at risk to high doses of radiation [14]. Chordoma represents one of the most common tumors treated with carbon ions radiotherapy (CIRT) [12,15].

The purpose of this study was to compare Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [16] with volume modifications for the evaluation of the response in patients with sacral chordoma not suitable for surgery and treated with CIRT alone. Furthermore, we aimed at verifying the correlation of patients' pain before and after treatment with the dimensional variations of chordomas. Finally, preliminary examinations were performed in order to detect if baseline Apparent Diffusion Coefficient (ADC) values, obtained from Diffusion Weighted Imaging (DWI), could predict response to treatment.

Materials and methods

Population

In this retrospective study we included 39 patients treated with CIRT alone, using active scanning beam delivery system at CNAO (CNAO, Centro Nazionale di Adroterapia Oncologica) of Pavia (Italy) from March 2013 to March 2016. All patients had biopsy proven sacrococcygeal chordoma; they were judged unresectable, and they were consequently treated with a total dose of 70.4 Gy equivalents (GyE) in 16 fraction. Every patient gave an informed consent to the procedure having a personalized treatment plan. Patients with residual sacral chordoma after surgery or with relapse after any other treatments or treated with protons were excluded from the analysis.

If the disease relapsed and patients were consequently scheduled for a second cycle of CIRT, only the follow-up exams before the re-irradiation were considered.

Imaging protocol and processing

Every patient performed a baseline MR exam; during the first year after the end of CIRT, MR examinations were scheduled three-monthly, then biannually.

All the MR exams were performed with the same 3 Tesla MR scanner (Magnetom Verio, Siemens Healthineers), using the following sequences:

- T2-weighted Turbo Spin Echo (TSE) on axial, sagittal and coronal plane, with Fat Saturation (FS);
- T1-weighted TSE on axial plane;
- Echo-planar imaging two-dimensional (Ep2d) Diffusion Weighted Images DWI – (b values 50, 400 and 1000 s/mm^2) on axial plane;
- T1-weighted TSE FS on axial, sagittal and coronal plane after intravenous paramagnetic contrast agent administration.

For each examination, T2w FS axial images were used both to measure lesion maximum diameter and to get a manual segmentation of the tumor using ITK-SNAP open source software (ver. 3.4.0-rcl). The lesion volume was then computed as the integral of the contoured voxels.

RECIST 1.1 [16] were used to evaluate chordoma response to CIRT, measuring the maximum lesion diameter on T2w FS axial sequences.

Similarly, the same response criteria were applied to volume modifications for treatment response evaluation. In particular, lesions presenting a volume reduction of at least 30% from the baseline were considered as a partial response; lesions presenting an increase of 20% of it were considered as a progression of disease; lesions between those two limits were considered as stable disease.

Furthermore, the segmented lesion was rigidly registered onto the Apparent Diffusion Coefficient (ADC) maps obtained from DWI sequences by means of dedicated Matlab tools (Version: R2010a, The MathWorks, Inc., Natick, MA, USA). In particular, the T2-weighted MR volume was registered onto the ADC map, and the computed transform was applied to warp consequently the segmented lesion. The ADC distribution, within the tumor, was finally characterized by means of the following histogram parameters: median, kurtosis, and skewness values.

The Numerical Rating Scale (NRS) was used to measure the painful symptomatology felt by patients, relying on a semiquantitative method based on 11 crescent numeric values, from 0 (total absence of pain) to 10 (the maximum pain imaginable by the patient) [17]. These measures were obtained at baseline evaluation and at the last available follow-up. For this evaluation patients were divided in two subgroups, depending on whether the upper limit of their chordoma was above or below S2–S3 space at baseline MRI.

Statistical analysis

Linear Mixed Models (LMM) were used to analyze diameter and volume changes during follow-up, in which relative date (number of days from the end of CIRT) was a fixed effect and patient identity was a random effect; this allowed to estimate the variability due only to the patient and not directly to the treatment, improving power and precision of the statistical model.

Kaplan–Meier survival analysis was used to estimate rates of local recurrence of disease.

Correlation between NRS and the response measured at the end of the follow-up in terms of diameter and volume was analyzed with a covariance analysis (ANCOVA) in which the chordoma upper limit was inserted as a factor.

All aforementioned analyses were performed using the software R (ver. 3.3.2, R core Team, 2017) and data reported correspond to means and standard errors.

Results

39 patients, 15 females and 24 males with a mean age of 63 years (range 38–84), met the enrollment criteria and were included in the study. They performed baseline MR exams and several follow-up controls after the end of CIRT, from 3 to 37 months afterward (mean time: 18 months), for a total of 195 examinations.

RECIST 1.1 vs volumes

At baseline examinations, the mean value of maximum axial lesion diameter was 96.9 mm (range: 44–260 mm); the mean lesion volume was 400.6 cm^3 (range: 9.1–2418.1 cm^3). At the last available follow-up, the mean value of maximum axial lesion diameter was 99.2 mm (range: 46–250 mm); the mean lesion volume was 297.5 cm^3 (range: 7.5–2341.4 cm^3). LMM analysis showed a significant lesion volume reduction during follow-up ($\beta = -0.035 \pm 0.008$, $X^2 = 21.089$, d.f. = 1, $p < 0.001$) [Fig. 1a], while there was not a significant variation of maximum diameter ($\beta = -0.0053 \pm 0.0041$, $X^2 = 1.696$, d.f. = 1, $p = 0.19$) [Fig. 1b]. Patient random effect was highly significant (LR-$X^2 = 74.369$, d.f. = 3, $p < 0.001$) and it explained about 45% of the total variability observed in the volume with the progress of follow-up.

Local recurrence was low, as Kaplan-Meier models showed more than 90% of patients free from disease recurrence after six

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