Radiotherapy and Oncology 120 (2016) 313–319

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate particle therapy

Dynamic contrast enhanced MRI monitoring of primary proton and carbon ion irradiation of prostate cancer using a novel hypofractionated raster scan technique

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ARTICLE INFO

Article history:
Received 24 March 2016
Received in revised form 13 May 2016
Accepted 15 May 2016
Available online 26 May 2016

Keywords:
Prostate cancer
Radiation therapy
Dynamic contrast enhanced MRI
Particle irradiation
Proton irradiation
Carbon ion irradiation

ABSTRACT

Purpose: To characterize parametric changes measured by sequential dynamic contrast enhanced perfusion MRI (DCE-MRI) during primary proton and carbon ion irradiation of prostate cancer using a novel hypofractionated raster scan technique to determine the potential of pharmacokinetic analysis for monitoring treatment effects of this novel irradiation scheme.

Materials and methods: Ninety-two patients were evaluated prospectively with DCE-MRI at baseline, day 10 during therapy, and 6 weeks, 6 months and 18 months after treatment completion. After motion correction and co-registration to morphological T2-weighted images, tumors and normal appearing contralateral parenchyma (NACP) were segmented manually on T2W images and ROI statistics calculated for pharmacokinetic parameters K^{trans}, k_{ep} and v_e using the standard Tofts model.

Results: The volume transfer constant (K^{trans}, $p < 0.001/p = 0.010$) and the leakage space partial volume (v_e, $p < 0.001/p = 0.005$) showed a statistically significant increase during therapy with protons and carbon ions, respectively. Parametric increases occurred only in patients naive to antihormonal therapy (AHT), and were maximal 10 days after the begining of treatment. The rate constant (k_{ep}) showed a significant increase only for proton, but not for carbon irradiation ($p = 0.021$). Statistically significant differences between PC and NACP were observed for all parameters ($p < 0.001$). AHT naïve patients with persistent PSA elevation above 1 ng/ml at 12 months experienced statistically significant elevation of K^{trans} and v_e compared to those with PSA suppression ($p = 0.04/p = 0.023$).

Conclusion: DCE parametric changes following ion particle irradiation of the prostate have not been previously reported. Their development into potential non-invasive imaging biomarkers for assessment of treatment response and efficacy is expected to be aided by the data on the magnitude and temporal evolution of parametric responses of cancer and normal tissue during and after therapy presented here, especially the changes of K^{trans} and v_e during therapy and their different measurement levels within tumors and in normal appearing contralateral tissue.

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The Ion Prostate Irradiation (IPI) pilot study is a prospective randomized phase II study, which examines the safety and feasibility of primary proton and carbon ion irradiation of the prostate using a hypofractionated raster scan technique [1]. Radiation therapy planning for the prostate entails carefully balancing intended treatment effects and toxicities, where most of the latter arise from non-target irradiation to the neighboring organs (specifically rectum and bladder). In the IPI study, several approaches are combined to maximize target organ specificity of radiation treatment: (i) Intensity modulated radiotherapy allows a dose increase to the target organ at unchanged toxicities compared to 3D conformal radiotherapy [2]. While almost all studies of ion irradiation have used passive beam modulation, the IPI study uses ion radiation with active beam modulation in a raster scan technique [3]. (ii) Compared to photons, the use of proton or carbon ion irradiation can further decrease the radiation dose exposure to normal tissue surrounding the target organ. This is mostly due to the ability to reduce dose exposure to the posterior wall of the rectum for protons [4] and carbon ions [5]. (iii) Hypofractionation of radiation treatment leads to increased dose at individual treatments while shortening the overall treatment time. Prostate cancer is one of the few neoplasms with a relatively low α/β value (1.5 Gy), indicat-

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http://dx.doi.org/10.1016/j.radonc.2016.05.012
0167-8140/

ing a late response to irradiation and resistance to low irradiation doses. Compared to the α/β values of bladder ($\alpha/\beta = 4.0$) and rectum ($\alpha/\beta = 3.9$), dose escalation by hypofractionation will increase chances for recurrence free survival at similar toxicity [6]. Primary endpoint of the IPI study is the proportion of enrolled patients who do not experience grade III and IV NCI-CTCAE (v. 4.02) (National Cancer Institute Common Terminology Criteria for Adverse Events) [7] toxicity and/or do not drop out from the therapy arm due to any reason. Grade III toxicity is defined as severe or medically significant but not immediately life-threatening, requiring hospitalization or prolongation of hospitalization, disabling or limiting self care activities of daily living. Grade IV toxicity is defined as life-threatening consequences requiring urgent intervention. Secondary endpoints are PSA-progression free survival (PSA-PF, overall survival (OS) and quality-of-life (QoL).

Furthermore, patients in the IPI study were monitored with multiple prostate MRI examinations. To the knowledge of the authors, prospectively acquired DCE-MRI data during primary proton and carbon ion hypofractionated raster scan technique irradiation to the prostate have not been previously reported. Thus, the purpose of this work is to report the effects of ion irradiation according to the IPI protocol on parameters measured with dynamic contrast-enhanced (DCE) MRI of the prostate.

Materials and methods

Patients and methods

Prospective data acquisition as part of the Ion Prostate Irradiation (IPI) study was approved by the local ethics committee of the University of Heidelberg (ethics approval number: S-298/2011) and informed consent was obtained from all participants. A total of 92 Patients were enrolled according to the study protocol in the period between March 2012 and October 2013, and acquisition of 12-month follow-up examinations was finished in December 2014. Patients were eligible for the study if they met the following inclusion criteria: (a) biopsy-proven PC with Gleason scoring, (b) less than 15% risk of lymph nodal dissemination according to the Yale formula [8], (c) Karnofsky performance scale index of $\geqslant$70%, (d) age between 40 and 80 years and (d) known PSA baseline measurement before the start of antihormonal therapy (AHT). Enrollment exclusion criteria were (a) presence of stage IV disease (distant metastases), (b) nodal positive disease, (c) hip endoprosthesis or other implants that would impair pelvic MR imaging, (d) prior pelvic irradiation, (e) participation in another clinical trial and (f) medical implants not cleared for ion irradiation during the study period (e.g. pacemaker, defibrillator). After initial enrollment, patients were excluded if (a) the patients requested their release from study participation before the study protocol was started ($n = 4$) or if (b) patients developed prostatitis after initial biopsy, precluding accurate initial imaging ($n = 3$). In total, 85 PC patients receiving Ion Prostate Irradiation were included in this study. Baseline epidemiological and clinical characteristics are shown in Table 1.

Patients were stratified into treatment arms of proton and carbon ion beam therapy at equal numbers. The radiation protocol used hypofractionated application of ion beam radiation at 20 individual irradiations, applied in batches of six radiation treatments per week.

MR imaging

Images were acquired using 1.5–3 Tesla MR systems (Magnetom Biograph mMr, Trio and Symphony, Siemens Healthcare, Erlangen, Germany) according to ESUR guidelines using an 18-channel body coil and a spine coil. Prior to dynamic imaging, pre-contrast T2-weighted TSE sequences were acquired in transverse, sagittal and coronal orientation (FOV = 200 – 300 × 200 – 300 mm^2, matrix = 244 – 430 × 220 – 375, TR > 5100 ms, TE > 105 ms). DSC-MRI was performed with a T1-weighted transverse time-resolved angiography with interleaved stochastic trajectories (TWIST) sequence during the bolus injection of a standard weight-adapted dose of 0.1 mmol/kg bodyweight of intravenous Gadobutrol (Bayer Schering Pharma, Berlin, Germany) at an injection rate of 3 ml/s. 40 slices with a thickness of 3 mm were acquired (FOV = 400 × 275 mm^2, matrix = 256 × 176, TR > 4.42–4.76 ms, TE = 1.72–2.2 ms). In total, 45–55 dynamic images were acquired in each slice at a temporal resolution of 5.6 s. MR imaging was performed at baseline, and then scheduled for the following additional timepoints: 10 days into therapy, and 6 weeks, 6 months and 18 months after therapy. The 10 day MRI represents the midpoint of radiation treatment, at which half of the dose has been applied to the target. Radiation doses were the same for all patients and for both types of heavy ion irradiation.

Table 1
Epidemiological and clinical characteristics.

Parameter	*n*
Age (yrs)	
Median (range)	66 (50–80)
Primary treatment (*n* (%))	
Prostate ion irradiation	
Proton irradiation	42 (49)
Carbon irradiation	43 (51)
Gleason-score (*n* (%))	
2 + 3	2 (2)
3 + 3	32 (38)
3 + 4	25 (29)
4 + 3	20 (24)
4 + 4	6 (7)
Duration of radiotherapy (days (range))	25 (13–31)
Interval (initial diagnosis – MRI) (days (range))	
Baseline MRI to start RT	15 (0–48)
Start RT to 1st follow-up (“10 day study”)	13 (4–21)
End RT to 2nd follow-up (“6 week study”)	44 (33–71)
End RT 3rd follow-up (“6 month study”)	185 (142–236)
End RT 4th follow-up (“18 month study”)	547 (365–747)
PSA measurement, median (IQR)	
Baseline	7.6 (4.5–10.6)
4 weeks	7.2 (4.6–10.3)
6 weeks	3.1 (1.9–5.2)
6 months	1.9 (0.9–3)
12 months	1.1 (0.6–1.9)
Antihormonal therapy at baseline [*n*/total (%)]	
Proton treatment	8/42 (19)
Carbon ion treatment	9/43 (21)

Abbreviations: MRI = magnetic resonance imaging; RT = radiotherapy.
Annotation: Values are median and range.

Image post-processing and analysis

All acquired baseline prostate MR examinations were reviewed clinically by experienced uroradiologists with 7 and >9 years of experience in prostate MRI (MR) to allocate the index lesion according to the findings of the sextant biopsy protocol. Post-processing of DSC-MRI data was then performed with Watson Elementary software (Watson Medical, Nijmegen, Netherlands), which incorporates a multi-step automated analysis of multi-parametric MRI data, including pharmacokinetic modeling of DCE data. For the analysis, T2w, DWI and DCE data were imported in DICOM format, and automatically co-registered using a nine degree of freedom affine transformation model in combination with a mutual information metric based on Parzen histograms [9], resulting in a voxel-wise matching of the imported sequences. A spoilt gradient echo sequence was used to measure dynamic con-