Radiotherapy and Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer

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ARTICLE INFO

Article history:
Received 11 May 2017
Received in revised form 23 July 2017
Accepted 27 July 2017
Available online xxxx

Keywords:
MR-guided
Stereotactic
Pancreas
Online
Adaptive
Planning

ABSTRACT

Background and purpose: To implement a robust and fast stereotactic MR-guided adaptive radiation therapy (SMART) online strategy in locally advanced pancreatic cancer (LAPC).
Material and methods: SMART strategy for plan adaptation was implemented with the MRIdian system (ViewRay Inc.). At each fraction, OAR (re-)contouring is done within a distance of 3 cm from the PTV surface. Online plan re-optimization is based on robust prediction of OAR dose and optimization objectives, obtained by building an artificial neural network (ANN). Proposed limited re-contouring strategy for plan adaptation ($SMART_{3CM}$) is evaluated by comparing 50 previously delivered fractions against a standard (re-)planning method using full-scale OAR (re-)contouring (FULLOAR). Plan quality was assessed using PTV coverage ($V_{95\%}$, D_{mean}, D_{1cc}) and institutional OAR constraints (e.g. V_{33Gy}).
Results: $SMART_{3CM}$ required a significant lower number of optimizations than FULLOAR (4 vs 18 on average) to generate a plan meeting all objectives and institutional OAR constraints. PTV coverage with both strategies was identical (mean $V_{95\%}$ = 89%). Adaptive plans with $SMART_{3CM}$ exhibited significant lower intermediate and high doses to all OARs than FULLOAR, which also failed in 36% of the cases to adhere to the V_{33Gy} dose constraint.
Conclusions: $SMART_{3CM}$ approach for LAPC allows good OAR sparing and adequate target coverage while requiring only limited online (re-)contouring from clinicians.
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Adaptive radiotherapy (ART) entails adjusting treatment plans in response to specific anatomic and/or biological changes which may occur during the course of the treatment. The ideal method to account for inter-fractional changes is to adapt treatment plans based on the anatomy of the day, which can be performed either offline or online [1,2]. Online plan adaptation needs to be performed fast with the patient in treatment position [3–5]. In recent years, several studies have shown the dosimetric benefit of treatment plan adaptation for tumour sites such as the cervix, prostate, bladder and pancreas [3,4,6–8], however, often using a library of plans and not based on the exact anatomy.

Upper abdominal tumours such as pancreatic cancer are particularly suitable for performing ART because of the proximity of several critical normal organs such as the duodenum, stomach and bowel. Daily variations in the position of the pancreas can be as large as 20 mm in all directions [9–12] and for the stomach even up to 35 mm [13]. In addition, mean displacements of the pancreas of 23, 11 and 7 mm in cranio-caudal, antero-posterior and lateral directions, respectively, due to breathing (intra-fraction motion) have been reported as well [14,15]. In recent years there has been growing interest in using hypofractionated radiation therapy, in particular stereotactic body radiotherapy (SBRT), for treatment of locally advanced pancreatic cancer (LAPC) [14–23]. IMRT techniques have been shown to reduce the dose to organs at risk (OAR) in pancreatic cancer [22,23], which is especially important for the duodenum, for which a significant correlation between the actuarial rates of grade ≥ 2 toxicity and dose has been reported [24,25].

The soft tissue contrast of available cone-beam CT scans is insufficient for ART in abdominal tumours. Magnetic-resonance imaging (MRI) offers superior anatomical imaging during the course of radiation therapy with the potential for improved delineation of the target volume and critical structures [26]. We recently implemented stereotactic MR-guided adaptive radiotherapy (SMART) for LAPC using IMRT with the MRIdian system (ViewRay Inc., Mountain View). This dedicated device combines a split-bore 0.35 T MR scanner with ^{60}Co radiation therapy (for a detailed description of the system see, for instance [27]). The system allows the acquisition of high-resolution volumetric MR images of the patient immediately prior to treatment, and

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http://dx.doi.org/10.1016/j.radonc.2017.07.028
0167-8140/

deformable image registration with automatic contour propagation to account for inter-fractional changes and plan adaptation based on the volumetric image of the day [28].

For a robust and fast online plan adaptation, we introduced an ART online strategy which can be performed within minutes, and which only requires limited (re-)contouring by the physician. The same beam parameters are used for plan (re-)optimization and optimization objectives rely on a model which predicts OAR dose as a function of distance from the target. To evaluate our online SMART strategy with limited (re-)contouring, we compared 50 completed ART fractions against a simulated standard (re-) planning method using full-scale OAR (re-)contouring, where optimization objectives were used for the entire OAR.

Material and methods

General SMART workflow for LAPC

The online SMART procedure for LAPC consists of three steps: 1) MR simulation during breath-hold, 2) deformation and adjustment of OAR contours and 3) online plan re-optimization. MR acquisition is performed during a 17 s breath-hold in shallow inspiration, using a FOV of 45 cm and 1.6 mm × 1.6 mm × 3 mm resolution. MR protocol for delineation is based on a true FISP sequence (Siemens) with a TR/TE of 3.83/1.62 ms and Flip Angle of 60°. The contours of the OAR, i.e. the duodenum, stomach, bowel and kidney are propagated from a pre-treatment MR simulation on the MRIdian to the MR of the day using deformable image registration and manually adjusted. ViewRay deformable registration uses an intensity-based algorithm which minimizes a cost function that measures the similarity between the images and it also uses a regularization term in order to obtain smoother deformation fields and prevent sharp discontinuities. The target volume is rigidly registered to the anatomy of the day and only edited when needed (for instance, in the case of rotations). The target volume (PTV) is generated from the GTV plus an isotropic 3 mm margin, excluding any possible overlap with OARs. In SBRT for LAPC in our institution which is performed under breath-hold conditions, CTV is considered to be equal to the GTV. Prescription dose is 40 Gy (95% isodose line) in 5 fractions and the plan is re-optimized for each fraction, allowing a D1% of PTV up to 50 Gy (125% of prescribed dose).

Treatment plans for LAPC are based on IMRT step-and-shoot and consist of 6 beam groups, with each beam group consisting of three equidistant beams at 60° separation in correspondence with the geometry of the three ^{60}Co sources on the gantry. During optimization, the optimizer can assign no fluence to a particular beam in case it turns out to be an unfavourable direction, according to the internal anatomy. Dose calculation is performed with a Monte-Carlo algorithm implemented in the MRIdian system with a statistical uncertainty of 1% and grid size of 0.3 cm × 0.3 cm × 0.3 cm by using the electron density map of the CT of the patient. At each fraction, the electron density map of the CT is deformed to the primary MR image representing the anatomy of the day, and it can be edited online before plan (re-) optimization if a discrepancy in air pockets or filling of OARs is detected. Before treatment delivery, patient-specific QA is performed with an independent Monte-Carlo dose calculation algorithm and gamma analysis.

Institutional OAR constraints for SMART for LAPC are: V_{33Gy} and V_{25Gy} less than 1 cc and 20 cc, respectively for duodenum, stomach and bowel. For the kidney and liver, the V_{12Gy} should be less than 25% and 50%, respectively. PTV coverage at 95% of prescription dose usually ranges from 85% to 95% depending on the vicinity of OARs and their geometry around the PTV, because OAR constraints have a higher priority than PTV coverage.

SMART strategy for daily plan re-optimization

The SMART strategy for online plan adaptation is based on the following components: 1) A robust baseline IMRT plan for online (re-)optimization is produced with the MRIdian planning system (see below, *Generating robust baseline plans*); 2) After deformation of contours at each fraction, OARs are reviewed and adjusted by the physician within a distance of 3 cm from the PTV; 3) OAR contours are subsequently spatially partitioned and combined in OAR portions located at 1, 2 and 3 cm from the PTV surface with the aid of a script for auto-contouring. Fig. 1 shows an example of this OAR partitioning and the cumulative OAR volume around the PTV at 1 (OAR_{1cm}), 2 (OAR_{2cm}) and 3 (OAR_{3cm}) cm distance from the PTV; 4) The plan is re-optimized with the same MRIdian planning software available at the treatment console, keeping the same beam parameters and optimization objectives (see below, *Generating robust baseline plans*). In summary, for each fraction, plan parameters and optimization objectives are kept unchanged and OAR_{1cm}, OAR_{2cm} and OAR_{3cm} structures used in the optimization are generated for each fraction according to the anatomy of that particular day.

Generating robust baseline plans

Robust and high quality baseline plans are generated using an in-house developed artificial neural network (ANN) approach (IBM SPSS Modeler v18, IBM®). To build this ANN (see also online Supplementary material), a total of 66 SBRT treatment plans for LAPC produced with the MRIdian treatment planning system were used as training plans, resulting in a model which predicts doses in OARs based on patient-specific geometric parameters. The following input parameters were used to build the ANN: PTV (cc), OAR_{1cm} (cc), OAR_{2cm} (cc), OAR_{3cm} (cc) and total patient-specific effective depth (cm) to the isocenter for all beams. Estimates of the median dose (D_{median}) at discretized portions of the OARs from 1 mm up to 50 mm distance from the PTV were generated as output parameters. These were also used as optimization objectives for OAR_{1cm}, OAR_{2cm} and OAR_{3cm} structures for plan (re-)optimization with the $SMART_{3CM}$ strategy to generate the SBRT plans (see Supplementary material). To generate all plans and achieve best dose gradients at the OARs, weights for optimization were manually obtained for each iteration by using the definition of the penalty function for OARs as implemented in the MRIdian TPS. ANN provided thus robust individualized optimization objectives according to patient-specific geometric parameters. All plans used to build the ANN were generated using our institutional constraints. This ANN model for dose prediction was validated on a total of 42 new SBRT treatment plans. Additional details about how the ANN for $SMART_{3CM}$ strategy was built are provided with the online Supplementary material.

Evaluation of SMART strategy for plan adaptation and statistical analysis

The developed SMART online strategy ($SMART_{3CM}$) for LAPC was evaluated against a standard (re-)optimization method using entire OARs for plan optimization (FULLOAR). As in the case of $SMART_{3CM}$, the definition of the penalty function for OARs as defined in the MRIdian TPS was used to achieve the best dose fall-off outside of the target. The only difference between $SMART_{3CM}$ and FULLOAR for plan generation is the use of OAR partitioning and of an ANN for dose prediction in $SMART_{3CM}$. Comparable baseline plans using both methodologies, fulfilling all institutional medical constraints were generated. For the adapted plans, full OARs were manually edited from the contour propagation, so also outside the 3 cm, in order to have a realistic comparison. For baseline planning, the number of

Please cite this article in press as: Bohoudi O et al. Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer. Radiother Oncol (2017), http://dx.doi.org/10.1016/j.radonc.2017.07.028