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Original article

Late toxicity in the randomized multicenter HYPRO trial for prostate cancer analyzed with automated treatment planning

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ABSTRACT

Purpose/objective: Assess to what extent the use of automated treatment planning would have reduced organ-at-risk dose delivery observed in the randomized HYPRO trial for prostate cancer, and estimate related toxicity reductions. Investigate to what extent improved plan quality for hypofractionation scheme as achieved with automated planning can potentially reduce observed enhanced toxicity for the investigated hypofractionation scheme to levels observed for conventional fractionation scheme.

Material/methods: For 725 trial patients, VMAT plans were generated with an algorithm for automated multi-criterial plan generation (autoVMAT). All clinically delivered plans (CLINICAL), generated with commonly applied interactive trial-and-error planning were also available for the investigations. Analyses were based on dose-volume histograms (DVH) and predicted normal tissue complication probabilities (NTCP) for late gastrointestinal (GI) toxicity.

Results: Compared to CLINICAL, autoVMAT plans had similar or higher PTV coverage, while large and statistically significant OAR sparing was achieved. Mean doses in the rectum, anus and bladder were reduced by 7.8 ± 4.7 Gy, 7.9 ± 6.0 Gy and 4.2 ± 2.9 Gy, respectively ($p < 0.001$). NTCPs for late grade $\geq$2 GI toxicity, rectal bleeding and stool incontinence were reduced from 23.3 ± 9.1% to 19.7 ± 8.9%, from 9.7 ± 2.8% to 8.2 ± 2.8%, and from 16.8 ± 8.5% to 13.1 ± 7.2%, respectively ($p < 0.001$). Reductions in rectal bleeding NTCP were observed for all published Equivalent Uniform Dose volume parameters, *n*. AutoVMAT allowed hypofractionation with predicted toxicity similar to conventional fractionation with CLINICAL plans.

Conclusion: Compared to CLINICAL, autoVMAT had superior plan quality, with meaningful NTCP reductions for both conventional fractionation and hypofractionation schemes. AutoVMAT plans might reduce toxicity for hypofractionation to levels that were clinically observed (and accepted) for conventional fractionation. This may be relevant when considering clinical use of the investigated hypofractionation schedule with relatively high fraction dose (3.4 Gy).

Prostate cancer is the second most common cancer in men worldwide [1]. External beam radiation therapy (EBRT) is one of the primary treatment modalities for patients with localized or locally advanced prostate cancer [2,3]. In the last decade, substantial improvements in EBRT techniques have been made, resulting in significant improvements in the treatment of prostate cancer patients [4–7]. Dose escalation has significantly improved treatment outcome in patients with localized prostate cancer [6,7]. However, this was often associated with a significant increase in toxicity [7,8], including rectal bleeding, fecal incontinence and changes in bowel habits [9]. Between 2007 and 2010, the randomized phase 3 multicenter HYPRO trial for intermediate- or high-risk localized prostate cancer investigated whether hypofractionated EBRT (19 fractions of 3.4 Gy) could improve relapse-free survival without increasing toxicity, compared to conventionally fractionated radiotherapy (39 fractions of 2.0 Gy) [10–12].

Since the end of patient accrual for the HYPRO trial, important improvements have been reported in treatment planning, in particular related to automated treatment plan generation. In Rotterdam, Erasmus-iCycle has been developed for fully automated, multi-criterial generation of Pareto-optimal plans with clinically desired balances between all treatment objectives [13,14]. The optimized Erasmus-iCycle plans are automatically reconstructed with the Monaco treatment planning system (TPS) (Elekta AB,

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Stockholm, Sweden) to generate clinically deliverable plans [15–18]. Compared to manual trial-and-error planning, automated planning has improved plan quality and consistency and drastically reduced treatment planning workload [15–18].

Aluwini et al. observed enhanced late toxicity in the hypofractionation arm of the HYPRO trial compared to conventional fractionation [11]. In this study, Erasmus-iCycle/Monaco was used to automatically generate deliverable treatment plans for HYPRO patients and compare them with the actually delivered, manually generated plans. As hypofractionation has logistic advantages for both the patient and the treatment center, we also investigated whether replacement of CLINICAL planning for hypofractionation by automated planning could avoid toxicity increases relative to accepted toxicity for conventional fractionation with CLINICAL planning. Apart from using dose volume histogram (DVH) parameters, analyses were also based on calculated normal tissue complication probabilities (NTCP) for late gastrointestinal (GI) toxicity.

Materials and methods

Patients and clinical treatment plans

Between 2007 and 2010, in total 820 patients with intermediate- or high risk prostate cancer were included in the HYPRO trial by seven Dutch radiotherapy centers. Patients were randomized to receive 78 Gy in 39 fractions (5fr/wk) (conventional fractionation), or 64.6 Gy in 19 fractions (3fr/wk) (hypofractionation) [10–12]. Three treatment groups were defined based on the risk of seminal vesicles' involvement. For group 1, the clinical target volume (CTV) consisted of the prostate only to be treated to the prescribed dose. For group 2, the prostate was treated to the prescribed dose, while the seminal vesicles were treated to a lower dose. For group 3, both the prostate and the seminal vesicles were treated up to the prescribed dose [10]. Patients were treated with a simultaneous integrated boost technique (SIB), either for dose reduction in the seminal vesicles (group 2) and/or for delivery of part of the dose with a reduced planning target volume (PTV) margin (all groups). For the large target (PTV_2), the prescribed dose was then reduced to 72.15 Gy in the conventional fractionation arm or 57.76 Gy in case of hypofractionation, instead of 78 Gy or 64.6 Gy as used for the boost (PTV_1). Depending on the set-up verification and correction strategy used in each participating institute, margins of 3–10 mm were added to the clinical target volume (CTV) (equal in both groups), yielding the PTVs. For the boost, it was allowed to reduce the margin toward the rectum to 0 mm. All centers applied the same dose constraints. The rectal volume receiving $\geq$ 65 Gy (EQD_{2Gy} for $\alpha/\beta = 3$Gy) had to be < 50%, and the anal mean dose < 60 Gy (EQD_{2Gy}). For bladder and femoral heads no constraints were specified [10].

A total of 725 HYPRO patients had evaluable clinical treatment plans, including scans, doses, and contoured structures, and could be included in this study. 361 patients were treated with conventional fractionation (75 in group 1, 219 in group 2, and 67 in group 3), and 364 patients were treated with hypofractionation (73 in group 1, 219 in group 2, and 72 in group 3). Of the included patients, 95.6% was treated using intensity modulated radiotherapy (IMRT) with 5–15 beams (median: 7 beams); the remainder with volumetric modulated arc therapy (VMAT). In all cases, a multi-leaf collimator (MLC) with a leaf width of 1 cm was used. In 96.4% of the plans, 10 MV photon beams were applied, in 3.2% 18 MV photon beams, and for the remainder, 6 MV photon beams. The treatment plans used in this trial ('CLINICAL' plans) were generated with conventional, interactive trial-and-error planning (designated in this paper by 'manual planning'), using the Monaco or Pinnacle TPS.

autoVMAT vs. CLINICAL

For each of the included patients, Erasmus-iCycle/Monaco was used to fully automatically generate a treatment plan for a modern treatment technique and modern equipment, i.e. VMAT at an Elekta Synergy treatment machine (Elekta AB, Sweden), equipped with an Agility MLC with 160 leaves of 0.5 cm in width ('autoVMAT'). Like for the vast majority of CLINICAL plans (above), a 10 MV photon beam was used. The autoVMAT plans were compared with the CLINICAL plans.

Although most of the included HYPRO patients were treated with an IMRT plan (above), for automated planning we chose for VMAT, as this is currently the common treatment approach for prostate cancer in the Netherlands. For a subgroup of 60 patients, we investigated to what extent our conclusions regarding plan quality differences between CLINICAL and automated planning depended on the difference in treatment technique. For this analysis, we used a subgroup of 60 patients treated with IMRT, consisting of 10 randomly selected patients for the 6 combinations of treatment group/fractionation arm. Erasmus-iCycle/Monaco was also used to automatically generate an IMRT plan for the clinical beam configuration ('autoIMRT'). Because of clinically applied 1 cm leaves (above), for the same subgroup of 60 patients, VMAT plans for the MLCi2 collimator with a leaf width of 1 cm (Elekta AB, Sweden) were automatically generated as well, and compared with the autoVMAT plans for the Agility MLC with 0.5 cm leaves. For all included patients, the automatically generated plan(s) had the same clinical intent as the clinical plan, i.e., same fractionation, risk group, etc.

Generally applied dosimetric parameters such as PTV coverage, near-minimum and near-maximum PTV doses, and mean and maximum doses in organs at risk (OARs) were used for plan evaluation and comparison. In addition, assuming an α/β-ratio of 3 Gy, we evaluated the percentage of rectum volume receiving equivalent doses in 2 Gy fractions (EQD_{2Gy}) of more than 65 Gy and 75 Gy (V_{65GyEq} and V_{75GyEq}, respectively). The latter parameters are associated with grade $\geq$ 2 GI toxicity and rectal bleeding [9]. Differences in predicted NTCPs for late GI toxicity were also quantified (see below). To apply the models, for both fractionation schemes, rectal doses were first converted into equivalent doses for 2 Gy fractions (EQD_{2Gy}), using $\alpha/\beta = 3$ Gy.

Hypofractionation with autoVMAT vs. conventional fractionation with CLINICAL Plans

For comparison of plans for the two fractionation schemes, all rectal and bladder doses were first expressed in terms of EQD_{2Gy} using an α/β-ratio of 3 Gy. For the rectum, these doses were then used to compare predicted NTCPs, V_{65GyEq}, V_{75GyEq}, and D_{mean}. For the bladder, D_{mean} was calculated and compared.

NTCP modeling for late GI toxicity

Aluwini et al. [11] have described the late GI toxicity (follow-up > 3 months) as observed in the HYPRO trial. Late toxicity was scored at 6 months and at 1, 2, 3, 4 and 5 years after treatment by case report form according to criteria from the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) [19] and by patients' self-assessment questionnaires. Details are provided in a previous publication [11].

NTCP models for toxicity observed in the HYPRO trial were generated for grade $\geq$ 2 late GI toxicity, stool incontinence, stool frequency, rectal bleeding and GI proctitis, using delivered rectal dose distributions and reported toxicities of the included 725 HYPRO patients. For NTCP modeling, all rectal DVHs were first

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