



Long-term follow-up results of endorectal balloon-assisted helical tomotherapy for localized prostate cancer patients in the high-risk group of gastrointestinal adverse events

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ABSTRACT

Background: Endorectal balloon (ERB) has been shown to reduce rectal radiation dose and late gastrointestinal toxicities in patients with prostate cancer. However, the usefulness of ERBs for patients with prostate cancer whose rectal shape or size is suboptimal has not been investigated. The purpose of this study was to present the long-term follow-up results of ERB-assisted helical tomotherapy for localized prostate cancer patients whose initial radiation treatment planning (RTP) was unacceptable due to suboptimal rectal shape or size.

Materials and methods: Of 541 consecutive patients with localized prostate cancer, 10 were included in this study whose RTPs without ERBs did not meet dose constraints due to: 1) Intestinal intrusion, 2) Small rectum; or 3) Unstable rectal shape. We re-planned using ERBs and delivered 76 Gy in 38 fractions, and evaluated the long-term usefulness and safety of ERB-assisted helical tomotherapy.

Results: At a median follow-up of 109 months, there were no local recurrences of prostate cancer. The overall, cause-specific, and progression-free survivals at 10 years were 90.0%, 100%, and 83%, respectively. Adverse events of grade 3 or higher were not observed during or after ERB-assisted helical tomotherapy.

Conclusions: When intestinal intrusion, a small rectum, or an unstable rectal shape is an obstacle for administering helical tomotherapy, ERBs might be the solution.

Key words: prostate cancer; radiotherapy; complications

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Introduction

Helical tomotherapy (HT) can provide a high conformal dose distribution to the target with the binary multileaf collimator (MLC) and megavoltage CT (MVCT) guidance while minimizing the dose to the surrounding normal organs at risks (OARs) [1, 2]. HT is an arc-based approach to intensity modulated radiation therapy (IMRT) delivery. Prostate cancer is one of the most suitable

cancers for HT, and high safety and efficacy have been shown [3, 4]. In addition, SpaceOAR hydrogel spacer has been shown to reduce rectal radiation dose and late gastrointestinal toxicities, and these advantages were verified in observational studies in various radiotherapy types [5]. However, if the intestinal tract enters the vicinity of the seminal vesicles, or if the rectal caliber is too small compared to the prostate, or if the rectal shape is poorly reproducible, it may be difficult to treat prostate

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cancer safely even if SpaceOAR is implanted. We utilized an endorectal balloon (ERB) to solve these problems, and administered HT-IMRT to localized prostate cancer patients in the high-risk group of gastrointestinal adverse events.

The purpose of this study was to present the long-term follow-up results of ERB-assisted HT-IMRT for patients with localized prostate cancer whose initial radiation treatment planning (RTP) was unacceptable due to suboptimal rectal shape or size.

Materials and methods

Patients

This single-institution retrospective study was approved by the institutional review board. This is a retrospective chart review consisting of 541 consecutive patients with localized prostate cancer (cN0, cM0) who were treated with HT-IMRT from August 2009 to May 2012. In 10 of the 541 patients, the initial RTP did not meet the criteria set by our institution, so the ERB was inserted and the RTP was made again. The reason for using ERB was that the radiation dose limits for the rectum and other intestinal tracts were not met. Ten patients in the “high-risk group of intestinal adverse events” were treated with ERB-assisted HT-IMRT, and the long-term safety and efficacy of the treatment were studied.

Table 1 showed the characteristics of the patients in the high-risk group of intestinal adverse events. The median age was 73 years (range, 64–84), and the median initial prostate-specific antigen (PSA) was 38.3 ng/mL (range, 10.4–481.3). T stages were various with T2a (n = 1), T2b (n = 2), T2c (n = 2), T3a (n = 2), and T3b (n = 3) disease. One patient presented with Gleason score (GS) 6, 5 patients had GS 7, and 4 patients were diagnosed with GS 9. The number of patients with National Comprehensive Cancer Network (NCCN) low, intermediate, high-risk, and very high-risk was 0 (0%), 3 (30%), 4 (40%) and 3 (30%), respectively.

Eligibility criteria

The high-risk group of intestinal adverse events was defined as any one of the followings at the time of initial RTP without ERB: 1) Intestinal intrusion; the intestinal tract enters the vicinity of the seminal vesicles, 2) Small rectum; the rectal caliber is

Table 1. Characteristics of patients treated by endorectal balloon-assisted helical tomotherapy for localized prostate cancer

Characteristics	Values
Age (years)	73
Median (range)	(64–84)
PSA [ng/mL]	38.3
Median (range)	(10.4–481.3)
NCCN risk group	
Intermediate	3 (30%)
High	4 (40%)
Very high	3 (30%)
Reasons for using ERB	
Intestinal intrusion	3 (30%)
Large prostate	1 (10%)
Unstable rectal shape	6 (60%)

PSA — prostate-specific antigen; NCCN — National Comprehensive Cancer Network; ERB — endorectal balloon

Table 2. Dose-volume constraints for the planning target volume (PTV), rectum, colon, small intestine, bladder and femoral head

PTV	Dmax < 81.3 Gy, Dmin < 68.4 Gy
Rectum	D67% < 60 Gy, D33% < 66 Gy, D1% < 81.3 Gy
Colon	D67% < 45 Gy, D1% < 55 Gy
Small intestine	D67% < 40 Gy, D1% < 50 Gy
Bladder	D67% < 65 Gy, D1% < 81.3 Gy
Femoral head	D33% < 52 Gy, D1% < 65 Gy

Dmax — maximum dose; Dmin — minimum dose; Dx% — dose received by x% of total organ at risk (OAR) volume, where x% = 1, 33 and 67%

too small (major diameter < 2 cm) compared to the prostate (prostate volume > 100 mL), 3) Unstable rectal shape; the rectal shape is poorly reproducible due to the large diameter of the rectum (major diameter > 4 cm) even when laxatives were administered, and did not meet the dose constraints for organs at risk (OARs) set by our institution based on the reference values recommended by Emami et al. [6]. Dose-volume constraints for the planning target volume (PTV), rectum, colon, small intestine, bladder and femoral head are shown in Table 2. If the RTP was made again using ERB and the criteria shown in the Table 2 were not met, HT-IMRT was not performed.

ERB-assisted HT-IMRT

Patients diagnosed as being in the high-risk group of intestinal adverse events were given lax-

atives (0.75% sodium picosulfate hydrate 10 mL) 12 hours before RTP CT scan, and instructed to empty their bladder and rectum 90 minutes before RTP CT scan, and then ERBs (RadiaDyne, LLC, Houston, TX, USA) were inserted and RTP CT scan was performed. Every patient underwent a CT simulation scan with a slice thickness of 2.5 mm. We generated HT RTPs using the dedicated tomotherapy treatment planning station. Dose parameters for the PTV and the OARs were adjusted iteratively until all the values of the parameters shown in Table 2 were met. The prescription dose to 95% of the PTV (D95%) was 76 Gy, which was delivered in 38 fractions using MVCT-based image-guided HT (Hi-ART system, Accuray, Sunnyvale, CA, USA). In each treatment session, ERB was inserted into the rectum and inflated with the same amount of air as when RTP was made.

Outcome and toxicity assessment

Patients were seen by a radiation oncologist once a week during HT-IMRT, and three months and six months after HT-IMRT, and then every six months thereafter. A PSA blood test was performed three months and six months after HT-IMRT, and then every six months thereafter. Biochemical recurrence after HT-IMRT was defined as PSA increase 2 ng/ml higher than the PSA nadir value [7]. Radiation therapy-related toxicity was measured by a radiation oncologist using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0).

Statistical analysis

We used the Kaplan–Meier method to estimate the overall survival (OS), cause-specific survival (CSS), progression-free survival (PFS), and radiation therapy-related adverse event free survival (AEFS).

Results

Reasons for using ERB

Of the 10 patients in the high-risk group of intestinal adverse events, three were due to intestinal intrusion (Fig. 1A), one due to small rectum (Fig. 1B), and six due to unstable rectal shape (Fig. 1C). When we made RTP again using ERB, we were able to meet the radiation dose constraints in all cases and successfully performed HT-IMRT.

Efficacy and toxicity

At the time of this report, the median follow-up duration was 109 months; 1 recurrence and 1 death events were found in the entire study population. One patient who relapsed was found to have bone metastases 94 months after HT-IMRT and is being treated with hormone therapy. One patient died of heart disease 46 months after HT-IMRT, although there was no recurrence. OS, CSS, and PFS at 10 years was 90.0% (95% CI: 47.3–98.5), 100%, and 83% (95% CI: 27.3–97.5), respectively (Fig. 2A–C). In the evaluation of adverse events, one patient developed grade 2 rectal hemorrhage 46 months after treatment, and one patient developed grade 2 urinary retention after 60 months (Fig. 2D–E). Adverse events of grade 3 or higher were not observed during or after HT-IMRT.

Discussion

This study demonstrated the potential efficacy of ERBs in prostate cancer patients at high risk of intestinal adverse events with long-term follow-up data. The uniqueness of this study is that the use of ERBs was limited to three criteria: intestinal intrusion, small rectum, and unstable rectal shape. Previous studies have evaluated the usefulness of ERB in consecutive patients with localized prostate cancer and have shown excellent biochemical control rates with minimal toxicity [8, 9]. However, now that daily adaptive radiation therapy and SpaceOAR are being used, the optimal indications for ERB need to be considered [10–12].

There are several advantages to using ERBs in patients with localized prostate cancer. First, if there is seminal vesicle invasion and also intestinal intrusion in the vicinity of the seminal vesicle, the intestine cannot be separated from the PTV by any method other than ERB. By pushing up the intestinal tract with ERB, radiation therapy can be safely performed on tumors in the seminal vesicles. Secondly, since ERB is cheaper, simpler and less invasive than SpaceOAR, ERB may be a promising alternative to SpaceOAR. There have been no clinical trials directly comparing ERB and SpaceOAR, but both reduce intestinal toxicities to the similar degree [13]. Third, the same rectal shape and volume can be reproduced in each fraction of radiation therapy. The use of ERB eliminates the need for daily adaptive radiation therapy and may re-

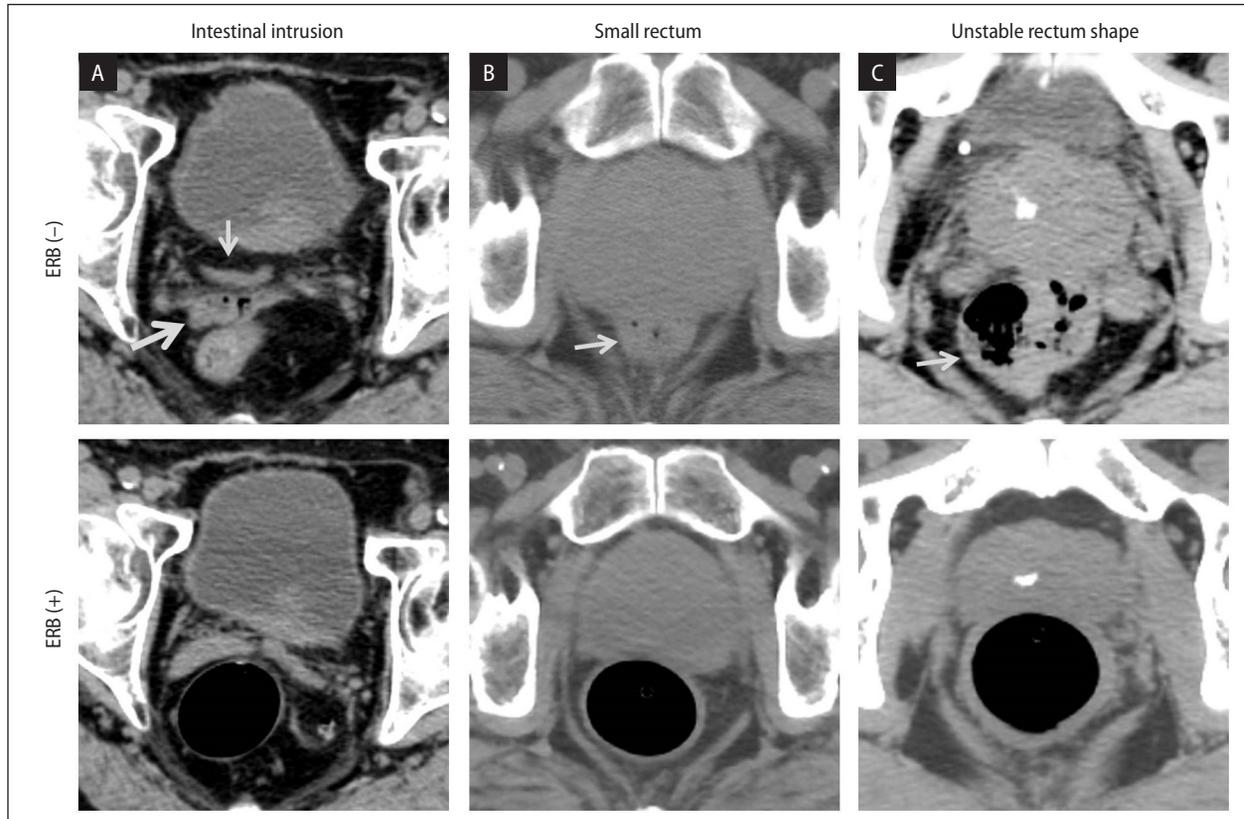


Figure 1. Representative cases of localized prostate cancer using endorectal balloons (ERBs) in the high-risk group of gastrointestinal adverse events. **A.** Intestinal intrusion. An 85-year-old very high-risk prostate cancer patient with seminal vesicle invasion. The initial radiation treatment planning (RTP) without ERB failed to meet the dose constraints due to the intestinal tract (large arrow) intruding near the seminal vesicles (small arrow). In the second RTP using ERB, the intestinal tract was pushed upwards, maintaining sufficient distance from the seminal vesicles; **B.** Small rectum. A 71-year-old high-risk prostate cancer patient made the initial RTP without ERB, but could not meet the dose constraints because the rectum (arrow) was too small compared to the large volume of the prostate. After 6 months of hormone therapy, the size of the prostate shrank slightly, but it was still over 100 mL. In the second RTP using ERB, most of the rectum was pushed backward, greatly reducing the rectal volume exposed to high doses of radiation; **C.** Unstable rectal shape. A 64-year-old intermediate-risk prostate cancer patient made the initial RTP without ERB. Even after laxatives were administered, stool and gas (arrow) stagnated in the rectum, and the shape and position of the rectum was not consistent. In the second RTP using ERB, the shape and position of the rectum became consistent as ERB was inserted in place of stool and gas.

duce the margin of PTV because it also suppresses intestinal peristalsis.

There are several limitations in the present study. First, the number of patients and events was small. However, the study was originally selected from 541 prostate cancer patients, who could not receive HT-IMRT without using ERB. Since the analysis was conducted by selecting only those patients who were initially not eligible for HT-IMRT without using ERBs, it is an acceptable proof-of-principle method to demonstrate the feasibility of ERBs. Secondly, the HT-IMRT schedule delivered 76 Gy in 38 fractions over 7-8 weeks. When this clinical study began, it was a standard dose fractionation schedule, but now hypofrac-

tionated and stereotactic body radiation therapy are the norm. If radiation therapy-related toxicity is reduced by changing the shape and position of the rectum by using ERB, similar results are expected to be obtained with different dosage and fractionation schedules.

Conclusions

In conclusion, a single-institutional retrospective analysis cannot be generalized to others without further scientific validations; however, if intestinal intrusion, a small rectum, or an unstable rectal shape is an obstacle when administering HT-IMRT, ERBs might be the solution.

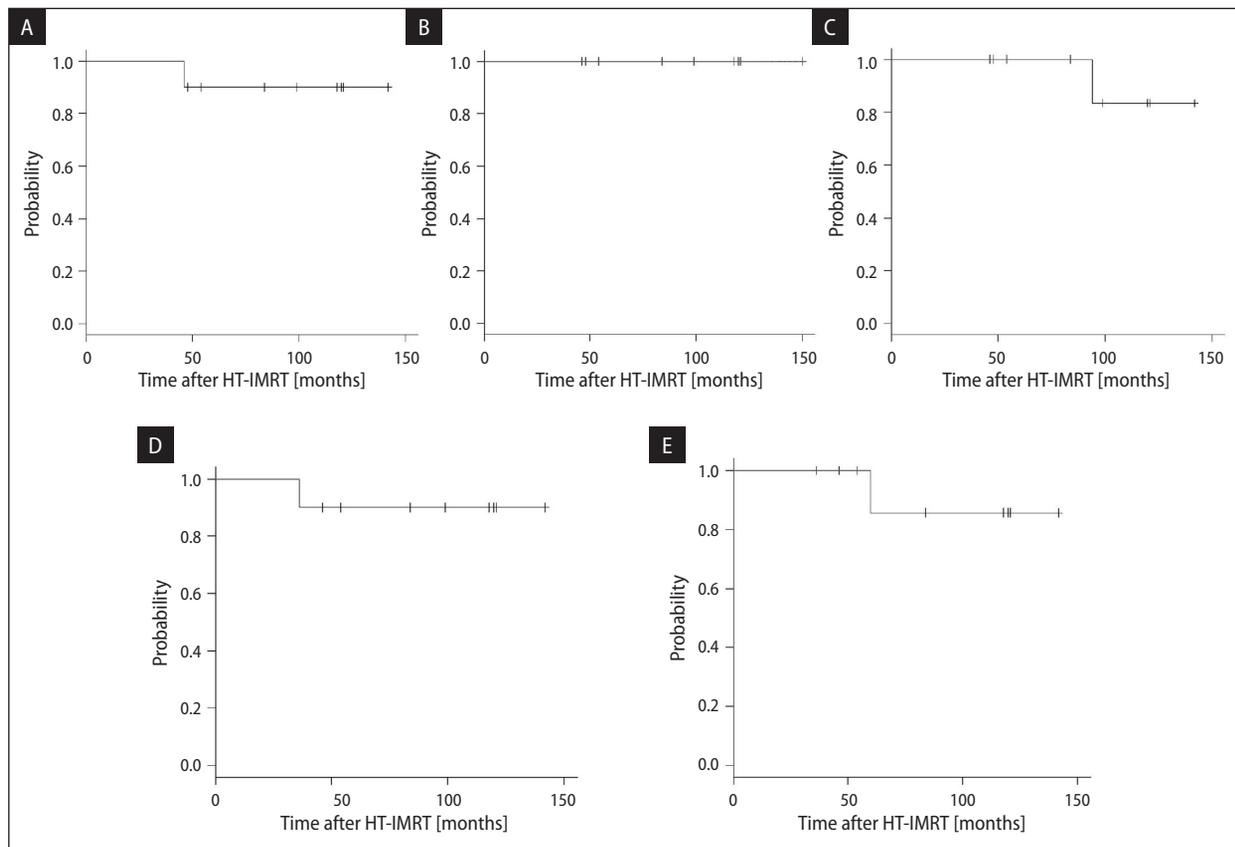


Figure 2. Kaplan-Meier estimates of survival. **A.** Overall survival; **B.** Cause-specific survival; **C.** Progression-free survival; **D.** Gastrointestinal adverse event free survival; **E.** Genitourinary adverse event free survival. HT-IMRT — helical tomography — intensity modulated radiation therapy

Conflict of interest

None declared.

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