Introduction

External beam radiation treatment is a well-established treatment modality for prostate cancer patients. Advancements in radiation treatment such as three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and proton therapy (PT) have allowed for highly conformal dose distribution to the target and consequently improved normal tissue sparing when dose escalation was performed. Radiation doses greater than 70 Gy have demonstrated greater local tumor control and improved biochemical outcomes, therefore delivery of higher doses of radiation has been attempted in order to further improve outcomes (1,2). Although a direct relationship between the level of dose administered and outcome has been shown, dose escalation in prostate cancer radiation therapy (RT) was traditionally limited by the associated rectal toxicities.

Due to prostate motion and setup uncertainties and to avoid significant deviation from the prescribed dose, planning target volume (PTV) margins are applied to the clinical target volume (CTV) to ensure dosimetric coverage of the prostate (3). The CTV-to-PTV margin may also increase the risk of irradiating surrounding normal tissues such as the rectum and may lead to increased anorectal...
Both et al. ERB in prostate radiotherapy

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As the use of ERBs expands, the need to reexamine its role in prostate RT becomes even more critical. A PubMed/MEDLINE search using the keywords: ERB, prostate RT, toxicities, real-time, IGRT, RGRT, and interfraction and intrafraction prostate motion was performed in order to identify new publications related to the use of daily-ERB for prostate RT since the review of Smeenk et al. (9). Ten prospective and retrospective ERB studies have since been published and form the basis of this review (8,10-18).

The issue of motion

Four of the ten studies pertain to the issue of prostate motion and are reviewed below (19-22). Radiofrequency-guided radiotherapy (RGRT) and image-guided radiation therapy (IGRT) have allowed for the use of advanced conformal RT techniques by monitoring interfraction and intrafraction tumor motion during treatment. IGRT utilizes specialized imaging such as a computed tomography (CT) scan, cone beam CT (CBCT) scan, ultrasound, or X-rays as a means to improve dose delivery. Technologies such as cine-magnetic resonance imaging (MRI), CT, and Calypso tracking systems (Calypso Medical Technologies Inc., Seattle, WA) have examined interfraction and intrafraction prostate motion, offline or online, relative to the patient treatment delivery. Calypso is the only in-beam real time tracking system which has been extensively used in the clinical setting for RGRT (19,20). Real-time prostate tracking during treatment delivery provides further insight into the role of daily-ERB in prostate intrafraction motion management.

Motion has been a critical factor during advanced
prostate RT and was previously, generally managed using external and internal immobilization devices. External anatomical variations are minimized by positioning the patient in a secure and reproducible manner based on indexed immobilization devices such as Knee-Lok and Foot-Lok cushions or personalized Vac-Lok body casts (CIVCO, Orange City, IA). Internal prostate fixation may be achieved using an air- or water-filled daily-ERB. Besides the external and internal immobilization devices, IGRT largely used in modern RT has been widely applied to prostate alignment based on implanted fiducial or prostate 3D representation.

Patient preparation for prostate RT may be particularly important as the prostate resides between organs with variable volumes such as the rectum and bladder. Intrafraction motion significantly hinders target localization as a result from rectal peristalsis, distention, and respiration (21,22). Studies using cine-MRI of non-ERB patient suggested that prostate motion is mostly due to the effect of gas pockets in the filled rectum (23).

The effect of stool and gas pockets on motion may affect the ERBs ability to reduce random intrafraction motions (10). Some advocate for patients’ pretreatment bladder and bowel preparations, such as daily use of anti-gas tablets with meals beginning 1-2 weeks prior, laxative suppositories or enemas within 1-4 hours prior, and voiding followed by immediately drinking adequate fluid (approximately 16 ounces of water) to achieve full bladder filling 20-30 min prior to CT simulation. Recently, Wootton et al. retrospectively examined the effectiveness of an ERB with passive gas release conduit on the removal of rectal gas for prostate proton radiotherapy. Two groups of fifteen patients treated with standard ERB and gas-release ERB were analyzed based on lateral kilovoltage (KV) images and the results showed that the mean incidence of gas in the anterior and other regions differed at a statistically significant level (11). Although the main limitation of this study was the lack of volumetric data, the possibility to identify the gas anterior to the ERB based on the lateral KV for a large number of fractions allowed the authors to conclude in favor of the use of the gas-release ERB for patients undergoing proton RT which mostly occurs with two parallel opposed beams. A potential advantage of a daily-ERB is that it allows for standardization of the rectal volume to minimize the daily variability of the prostate position, leading to improved target localization over the course of treatment (12).

As mentioned previously, 4 of the 10 recent reports have evaluated the effect of ERB on reducing prostate intrafraction motion via RGRT (10,12-14). Both et al. (13) prospectively studied real-time prostate intrafraction motion as a function of treatment time to determine an optimal IM for ERB patients and addressed the patient-specific intrafraction motion. A daily-ERB (RadiaDyne, LLC, Houston, TX) was filled with 100 cc of water. All patients received 79.2 Gy to the PTV in 44 fractions of 1.8 Gy per fraction via IMRT or Varian RapidArc (Varian2300IX; Varian Medical Systems, Palo Alto, CA). The balloon position relative to the rectum canal was ensured through the use of an indexed ERB, positioned based on the value obtained at the time of simulation. Calypso tracking system was utilized to evaluate three-dimensional (3D), lateral (L), cranial-caudal (CC), and anterior-posterior (AP) displacements for a group of 24 patients with a total of 787 tracking sessions. The average percentage of time with 3D, L, CC, and AP prostate displacements >2, 3, 4, 5, 6, 7, 8, 9, and 10 mm in 1 minute intervals was calculated for up to 6 minutes of treatment time. 3D analysis showed that prostate motion is dependent on treatment time for displacements >2, 3, and 4 mm. Interestingly, displacements >5 mm showed time-independence, and the larger motions >6 mm were negligible within 6 minutes treatment time. The overall average time with prostate displacement >3 mm was 5%, suggesting that a 3 mm IM would sufficiently cover 95% of the treatment time within a 6 minute interval. Moreover, for treatment times longer than 6 minutes, a 5 mm IM may be considered to cover more than 95% of time due to the time-independence of the motion >5 mm observed. Directional analysis shown in this study illustrated negligible lateral prostate motion while the AP and CC motions were comparable. The authors also indicated that no obvious relationship exists between the percentage of time at displacement and the week of treatment course, indicating the use of an ERB obviates the correlation between bowel habit changes and rectal volume over the treatment course. Their findings suggested that use of a daily-ERB consistently stabilized prostate motion and prevented clinically significant displacements to occur.

Following the study of Both et al. (13), Wang et al. (14) further compared the intrafraction motion between 30 (1,008 sessions) ERB and 29 (1,061 sessions) non-ERB patients groups. The same patient preparations described by Both et al. (13) were applied to both groups. Large 3D motion (up to 1 cm or more) was noted in the non-ERB group. The motion increased as a function of time for displacements >2-8 mm for the non-ERB group and >2-4 mm for the ERB group. The authors also indicated that the percentage time distributions
between the two groups were significantly different for motion > 5 mm. The 3D symmetrical IM can be reduced by 40% from 5 to 3 mm if an ERB is chosen as the internal immobilization device. Based on the similar directional analysis as described in Both et al. (13), this study showed that the percentage of time the prostate displaced in any direction was less in the ERB group than the non-ERB group, with a particularly large motion reduction shown in the anterior-posterior directions, which may allow for dose escalation while sparing surrounding normal tissues such as bladder and rectum (4, 24). The motion patterns of the patients representing the worst-case scenario for both groups were analyzed in this study, which found that the percentage time of prostate displacements > 3 up to 10 mm was consistently higher for the non-ERB patient group.

Smeenk et al. (10) investigated prostate intrafraction motion during RT and performed a one-to-one comparison of 15 ERB (567 sessions) to non-ERB patients (576 sessions). All patients received a total dose of 80 Gy in 2 Gy fractions and the ERB patients were applied with a 100 cc air-filled balloon (QLRAD B.V., Dalfsen, Netherlands). The intrafraction motions were analyzed in 150 second timeframes, using the Calypso system, at displacements > 1, 3, 5, and 7 mm for 3D vector analysis to determine where motion was most volatile. The analysis showed displacements < 5 mm were more frequent for both groups. However, after 150 seconds there was a linear increase of displacement with time, most notably for displacements > 3 mm. There were significantly smaller variances of the percentages of 3D displacement > 3, 5, and 7 mm when treated with an ERB. Intrafraction motion of 3D-vector deviations > 1, 3, 5, and 7 mm were 57.7%, 7.0%, 0.7%, and 0.3% in the ERB group vs. 70.2%, 18.1%, 4.6%, and 1.4% in the non-ERB group after 10 minutes. Prostate interfraction motion was evaluated and they found insignificant interfraction variation between cohorts with and without a daily-ERB but there were significantly less intrafraction motions with an ERB (10, 15). The data suggested a 5 mm IM to be sufficient for prostate intrafraction motion when using an ERB (10), as similarly indicated by Both et al. and Wang et al.

Hung et al. (12) investigated daily interfraction prostate motion comparing two cohorts of patients (14/15) treated with fiducial markers implanted in the prostate with and without daily-ERB. Based on portal imaging, the daily displacements necessary to place the prostate at the isocenter were determined and analyzed. The change in interfraction prostate motion over the course of treatment was reduced for the ERB group, however not statistically significant and therefore the use of daily image guidance was still recommended when daily-ERBs are employed.

**Dosimetric studies**

Two of the 10 recent reports have assessed the dosimetric consequences and potential benefit of ERB use. In the first, Smeenk et al. (15) investigated the dosimetric effect of the ERB on anorectal toxicities post-prostatectomy IMRT for 20 patients who underwent salvage IMRT treatment planning with a prescribed dose of 70 Gy with and without a 100 cc air-filled ERB (QLRAD B.V., Dalfsen, Netherlands). Comparative analysis reported significant reductions of the anal wall (Awall) dose-volume indicators except for V70Gy, while the mean dose was reduced by an average of 6 Gy. The rectal wall (Rwall) V30Gy, V45Gy, and A40Gy were found to be significantly reduced as well. According to this dosimetric study the use of an ERB has the potential to spare the anorectal wall and in particular the Awall in high-dose post-prostatectomy IMRT.

In the second dosimetric study, Tang et al. (8) conducted a detailed dosimetric comparison among anterior, anterior-oblique, and lateral passive scattering proton beams for 10 patients treated with a daily-ERB has shown that the anterior-oriented beams can fully exploit the sharp distal penumbra to spare the rectum and provide superior dose distribution. The rectal volume that receives 95% of the prescription dose in the anterior beams is about 1/10 of that in the lateral beams. The mean dose of rectum and penile bulb can also be reduced by about a factor of two. Femoral heads are not included in the anterior-oriented beams and hence received negligible dose but the bladder received a much higher dose in the anterior beams. However, an optimal plan can be produced to significantly reduce the rectal dose without compromising the bladder dose by properly weighting all the available beams. In addition, the introduction of anterior-oriented fields allows for the possibility of either reducing treatment toxicity at current prescription doses or further dose escalation in the treatment of prostate cancer.

In order to correct for range uncertainty due to bladder volume variability when anterior beams are employed an array of dosimeters can be placed on the anterior surface of the ERB for the purpose of range verification as well as dose monitoring during treatment (8). An in vivo range verification method particularly for the passive scattering delivery system has shown millimeter accuracy in phantom tests (25, 26). With a small amount of dose from a probing
beam delivered to the detectors at the beginning of the treatment, the residual range of the probing beam can be determined, which is then used to adjust the treatment beam. The pretreatment “range check” using detectors placed on the ERB makes the anterior-oriented proton beams clinically feasible and offer the ability to deliver improved dose distributions in proton prostate RT.

**Clinical outcomes**

The Smeenk et al. review (9) summarized the GI toxicity outcomes of patients treated with an ERB during radiotherapy for the potential benefit of prostate fixation, dose escalation, and anorectal sparing, as reviewed in Table 1, specifically for photon therapy. Since then 3 additional reports discussed below have examined clinical outcomes (20-22) in photon therapy. The first, also noted in Table 1, has reported clinical outcomes in terms of acute GI and GU toxicities using a water-filled ERB during IMRT (16).

Prostate proton therapy is delivered in conjunction with a water-filled daily-ERB to eliminate the dose heterogeneities in the beam. In contrast, photon radiation therapy reports indicate most commonly the use of air-filled ERBs for the benefit of anterior rectal wall sparing at the risk of diminished posterior target coverage. Song et al. (33) reviewed conventional treatment planning to address heterogeneity by comparing the dose calculations to a Monte Carlo simulation using the four-field box technique and found that the treatment planning system inferred higher dose regions resulting in potential under dosage of 3.4% mean dose for the posterior beam near the peripheral zone of the prostate, where up to 74% of the prostate cancer foci are located (34). Thus, a water-filled ERB, has more recently been employed during IMRT to reduce dose heterogeneity and potential dose calculation errors due to treatment planning algorithm limitations which could lead to diminished target coverage.

Deville et al. (16) reported the acute GI and GU toxicity rates for 100 prostate cancer patients undergoing image-guided intensity-modulated radiation therapy (IG-IMRT) with a daily endorectal water-filled balloon (ERBair), using an indexed-lumen 100 cc ERBair to 79.2 Gy in 1.8 Gy fractions. They found that Grade ≥2 GI and GU toxicity rates of 8% and 42%, respectively, compared favorably with (I) patients treated with IMRT using an ERBair - for which there is only a single institution data from the Baylor group, reporting rates of acute GI and GU toxicity of 18% and 35%, respectively, in 396 prostate cancer patients treated from 1997-2001 with mean dose 77 Gy (specifically 70 Gy in 2 Gy daily fractions prescribed to the 85% isodose line) IMRT using 100 cc ERBair (35) - and (II) with the more extensively reported acute GI and GU toxicity rates for non-ERB prostate IMRT including their own institution at 13% and 50%, respectively (36).

In an in-depth analysis of anorectal toxicity, Smeenk et al., recently investigated the relationship between anal and rectal DVH parameters and GI incontinence-related complaints such as urgency, incontinence, and frequency in 60 prostate cancer patients undergoing external beam RT (3- or 4-field 3DCRT or 5-field IMRT to 67.5 or 70 Gy in 2.25 or 2.5 Gy fractions) between 2000-2007 using anorectal manometry and barostat measurements to evaluate anal pressures, rectal capacity, and rectal sensory functions at least 90 days post-treatment (17). Half were treated with an 80 cc air-filled ERB. They found that in patients with (I) frequency - almost all rectal parameters were reduced, (II) urgency - several anal wall and rectal wall were predictive, such as the anal Dmean >38 Gy, and (III) incontinence - some anal wall parameters correlated. Patients treated with an ERB described significantly fewer complaints than patients treated without a balloon, which was therefore attributed to receiving lower doses to the Awall and Rwall.

In a related report, Smeenk et al., retrospectively investigated the relationship between fecal incontinence-related complaints and individual pelvic floor muscles (the internal anal sphincter (IAS) muscle, the external anal sphincter (EAS) muscle, the puborectalis muscle (PRM), and the levator ani muscles (LAM), in addition to the Awall and Rwall in 48 patients undergoing prostate radiotherapy (3- or 4-field 3DCRT or 5-field IMRT to 67.5 or 70 Gy in 2.25 or 2.5 Gy fractions), 28 patients with an 80 or 100 cc air-filled ERB (18). They found that urgency was associated with several anal and rectal wall parameters, as well as doses to all separate pelvic floor muscles, while incontinence was associated mainly with doses to the EAS and PRM. Based on the dose-effect curves, they suggested the following mean doses to reduce the risk of urgency: ≤30 Gy to the IAS; ≤10 Gy to the EAS; ≤50 Gy to the PRM; and ≤40 Gy to the LAM. Finally, similar to the previous study, they found that patients treated with an ERB reported significantly less urgency and incontinence, attributed to significantly lower doses to the Awall, Rwall, and all pelvic floor muscles.

**Conclusions**

The emerging evidence of the role of ERB in prostate RT...
Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Therapy</th>
<th>ERB</th>
<th>Follow-up</th>
<th>Toxicity</th>
<th>DVH parameters and/or correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>The (27)</td>
<td>116</td>
<td>IMRT 76 Gy (mean)</td>
<td>100 cc air-balloon</td>
<td>31.3 months (median)</td>
<td>GI: rectal</td>
<td>Rectal mean: V65 =16.5%</td>
</tr>
<tr>
<td>The (28)</td>
<td>40 PPI vs. 125</td>
<td>15 MV IMRT PPI: 64 Gy</td>
<td>100 cc air-balloon</td>
<td>Acute</td>
<td>GU: PPI vs. PI</td>
<td>Bladder: Dmean: PPI &gt; PI</td>
</tr>
<tr>
<td>Goldner (29)</td>
<td>399 of 486 enrolled prospective multicenter trial [1999-2002]</td>
<td>4 field 3DCRT Low-inter: 70 Gy High: 74 Gy 87% neoadjuvant, 7 months ADT</td>
<td>40 cc air PTV = CTV+10 mm (5 mm post after 66 Gy)</td>
<td>65 months (median)</td>
<td>GI: Late crude side effect Grade 2/3: 23%/2% 5 yr actuarial late side effect Grade ≥2: 28%/30% GU: Late crude side effect Grade 2-3: 16%/2% 5 yr actuarial late side effect Grade ≥2: 19%/34%</td>
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</tr>
<tr>
<td>Goldner (30)</td>
<td>166 (subset of 486) prospective multicenter trial [1999-2002]</td>
<td>4 field 3DCRT Low-inter: 70 Gy High: 74 Gy 87% neoadjuvant, 7 months ADT</td>
<td>40 cc air PTV = CTV+10 mm (5 mm post after 66 Gy)</td>
<td>Rectal sigmoidoscopy 12 and/or 24 months Median follow-up 40 months</td>
<td>GI: Late rectal toxicity: Grade 0: 57% Grade 1: 11% Grade 2: 28% Grade 3: 3%</td>
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<tr>
<td>Woel (31)</td>
<td>46 Prospective, phase II [2001-2003]</td>
<td>4 field 15 MV 3DCRT 72 Gy (95% iso) =75.6 Gy (1.8 Gy)</td>
<td>6 months ADT</td>
<td>60 cc air ERB first 15 treatments only. PTV = CTV +5 mm PTV without balloon = CTV +15 mm</td>
<td>Acute only (up to 3 months from end of treatment)</td>
<td>Acute: medical intervention (i.e., RTOG grade ³ 2 equiv.) GI: Loose bm 11%, hemnorhoidal 20% GU: 50% Anal cutaneous skin: 70% No significant difference by 3 months.</td>
</tr>
<tr>
<td>D’Amico (4)</td>
<td>57 Prospective, phase II [2001-2004]</td>
<td>4 field 15 MV 3DCRT 75.6 Gy (1.8 Gy)</td>
<td>6 months ADT</td>
<td>60 cc air ERB first 15 treatments only. PTV = CTV +5 mm PTV without balloon = CTV +15 mm</td>
<td>Minimum 1 yr follow-up, median 1.8, max 3.3.</td>
<td>GI: 2-yr estimate Grade 3 rectal bleeding 10%, all in patients on anticoagulation and controlled with argon plasma coagulation. Grade 1: 18% Rectal V70 median 3.7 cc</td>
</tr>
<tr>
<td>Van Lin (32)</td>
<td>48 ERB [24] vs. non-ERB [24] prospective, randomized [2002]</td>
<td>4 field 18 MV 3DCRT 67.5 Gy (2.25 Gy)</td>
<td>6 months ADT</td>
<td>80 cc air PTV = CTV +9 mm</td>
<td>30 months with repeat sigmoidoscopy at 3, 6, 12, 24 mo.</td>
<td>Acute GI: no Grade 3, non-ERB vs. ERB Grade 1: 50% vs. 46%, Grade 2: 29% vs. 29% (NS) Late GI: non-ERB vs. ERB Grade 1+ late rectal bleeding 58% vs. 21% (P=0.003) ERB decreased Rectal wall V40+, as well as the percentage of areas showing high grade telangiectasias at 2 years.</td>
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</table>

Table 1 (continued)
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<table>
<thead>
<tr>
<th>Study</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Deville (16)</td>
<td>100 retrospective</td>
<td>IG-IMRT</td>
<td>100 cc water-filled balloon</td>
<td>Acute only</td>
<td>GI: max Grade 0, 1, 2 was 69%, 23%, 8%</td>
<td>Infield rectum associated with mean/median doses, D75, V30, V40. Infield bladder V20 associated with Grade 2 GU toxicity.</td>
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<tr>
<td></td>
<td>[2008-2010]</td>
<td>79.2 Gy</td>
<td>PTV = CTV +10 mm, 6 mm post</td>
<td></td>
<td>GU: max Grade 0, 1, 2 was 17%, 41%, 42%</td>
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Abbreviations: ADT = androgen deprivation therapy; CTV = clinical target volume; DVH = dose-volume histogram; ERB = endorectal balloon; GI = gastrointestinal; GU = genitourinary; PI = primary; PPI = post-prostatectomy; PTV = planning target volume

Consist mainly of real-time tracking of the prostate motion with and without an ERB and showed a favorable reduction in the IM required when a daily-ERB was employed while the introduction of gas release ERBs seems promising. Dosimetric studies suggest improved dose distributions when the ERB is employed using parallel opposed beams and especially for anteriorly oriented beams with ERB guided range verification. The outcome study of Deville et al. presents promising finding for early GI toxicity with a water-filled ERB, however late toxicity data should be awaited. Correlative studies of late rectal function and anorectal dosimetry by Smeenk et al. provided clinical evidence for the dosimetric gains noted with an ERB. Further investigation of SV variation and involvement, rectal deformation, and stool and air contributions are merited and will likely comprise future directions.

**Acknowledgements**

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**References**

35. Bastasch MD, Teh BS, Mai WY, et al. Tolerance of