Transitioning from conventional radiotherapy to intensity-modulated radiotherapy for localized prostate cancer: changing focus from rectal bleeding to detailed quality of life analysis

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With the advent of modern radiation techniques, we have been able to deliver a higher prescribed radiotherapy dose for localized prostate cancer without severe adverse reactions. We reviewed and analyzed the change of toxicity profiles of external beam radiation therapy (EBRT) from the literature. Late rectal bleeding is the main adverse effect, and an incidence of >20% of Grade \( \geq 2 \) adverse events was reported for 2D conventional radiotherapy of up to 70 Gy. 3D conformal radiation therapy (3D-CRT) was found to reduce the incidence to ~10%. Furthermore, intensity-modulated radiation therapy (IMRT) reduced it further to a few percentage points. However, simultaneously, urological toxicities were enhanced by dose escalation using highly precise external radiotherapy. We should pay more attention to detailed quality of life (QOL) analysis, not only with respect to rectal bleeding but also other specific symptoms (such as urinary incontinence and impotence), for two reasons: (i) because of the increasing number of patients aged >80 years, and (ii) because of improved survival with elevated doses of radiotherapy and/or hormonal therapy; age is an important prognostic factor not only for prostate-specific antigen (PSA) control but also for adverse reactions. Those factors shift the main focus of treatment purpose from survival and avoidance of PSA failure to maintaining good QOL, particularly in older patients. In conclusion, the focus of toxicity analysis after radiotherapy for prostate cancer patients is changing from rectal bleeding to total elaborate quality of life assessment.

Keywords: prostate cancer; radiotherapy; rectal bleeding; incontinence; genitourinary symptom; erectile dysfunction

INTRODUCTION

Prostate cancer is one of the most prevalent solid tumors diagnosed in men in the USA and developed countries. Recent research in numerous randomized controlled trials demonstrated that increasing the prescribed dose in the treatment of localized prostate cancer improves biochemical control in several risk categories: low-, intermediate- and high-risk prostate cancer patients, at least for certain subgroups of patients, as summarized in two recent meta-analyses [1, 2] (Table 1). Consequently, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (2013) state that doses of 75.6–79.2 Gy in conventional fractions delivered to the prostate are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, a dose of up to 81.0 Gy provides improved prostate-specific antigen (PSA)-assessed disease control [3].

On the other hand, survival was at least as good as that expected for an age-matched group of patients from the general population [4]. The fact that elderly patients will die...
### Table 1. Conventional radiation therapy and 3D conformal radiation (3D-CRT) therapy

| Author (Institute) | Year (Pt No.) | Study | Follow-up (median) | Radiotherapy | PSA control rate* (L/I/H) | Adverse toxicity criteria | Adverse reaction Late G2 or more if otherwise cited |
|--------------------|---------------|-------|-------------------|--------------|--------------------------|--------------------------|---------------------------------|
| **Conventional 2D vs 3D-CRT** |
| Dearnaley [5] (UK) | 1999 (n = 225) | RCT: 2D vs 3D-CRT n = 111 vs 114 | 3.6 years | 64 Gy | 3.6 years 78% vs 83% | RTOG | GI 15% vs 5% P = 0.01 GU 23% vs 20% | 3D-CRT reduced GI toxicity |
| Koper [6] (Netherland) | 2004 (n = 248) | RCT: 2D vs 3D-CRT n = 125 vs 123 | 2 years (minimum) | 66 Gy | NA | RTOG modified score | late rectum 10% vs 7%, anus 2% vs 2%, bladder 11% vs 9% | 3D-CRT ≒ 2D at 66 Gy pre-existing/acute symptoms related to late reaction |
| Yoshioka [7] (Osaka Univ.) | 2013 (n = 362) | 2D vs 3D-CRT n = 127 vs 235 | 4.5 years | 70 Gy | NA | CTCAE v 4.0 | GI 23% vs 7% P < 0.001 | 3D-CRT reduced field widths and GI toxicity |
| **3D-CRT** |
| Kuban [8] (MDAC) | 2008 (n = 300) | RCT n = 149 vs 151 | 8.7 years | 70 Gy vs 78 Gy | 8 years 50% vs 73% P = 0.004 (63%/76%/26%) vs (88%/86%/63%) | RTOG/LENT | GI 13% vs 26% P = 0.013 GU 8% vs 13% | higher dose improved PSA control and elevated GI toxicity |
| Zietman [9] (MGH) | 2005 (n = 392) | RCT n = 197 vs 195 | 5.5 years | 70.2 GyE vs 79.2 GyE 3D-CRT 50.4 Gy + Proton Boost 28.8 GyE vs 19.8 GyE | 61.4% vs 80.4% P < 0.001 | RTOG | GI 9% vs 18% P = 0.005 GU 20% vs 21% | higher dose improved PSA control and elevated toxicity |
| Peeters [10] (Netherland) | 2006 (n = 664) | RCT: Dutch trial n = 331 vs 333 | 51 months | 68 Gy vs 78 Gy | 54% vs 64% P = 0.02 | RTOG/ EORTC modified | GI 27% vs 32% GU 39% vs 41% | higher dose improved PSA control higher dose elevated GI toxicity (25% vs 35%) at 7 years [11] |
| Dearnaley [12] (UK) | 2007 (n = 843) | RCT: MRC RT01 n = 421 vs 422 | 5 years | 64 Gy vs 74 Gy | 60% vs 71% P = 0.000 7 | RTOG | GI 24% vs 33% P = 0.005 GU 8% vs 11% | higher dose improved PSA control and elevated GI toxicity |
| Skwarchuk [13] (MSK) | 2000 (n = 743) | Dose escalation n = 96 vs 266 vs 320 vs 61 | 5 years | 64.8 Gy vs 70.2 Gy vs 75.6 Gy vs 81 Gy | NA | RTOG/ EORTC modified LENT/SOMA | GI 3.4% vs 7.8% vs 15.9% vs 16.5% | higher dose elevated GI toxicity |
| Pollack [14] (MDAC) | 2002 (n = 301) | RCT n = 150 vs 151 | 6 years | 70 Gy vs 78 Gy | 6 years 64% vs 70% P = 0.03 | RTOG | rectum 12% vs 26% P = 0.001 bladder both 10% | higher dose improved PSA control and elevated GI toxicity |
should be considered, if not from their prostate cancer, then from one of the many competing causes of death. Therefore, it is important to determine what could most likely cause their demise. In high-risk patients who are relatively younger (<70 years old at diagnosis), dose escalation leads to a much higher likelihood of dying of a cause other than cancer. Perhaps equally notable, patients who are aged >70 years during treatment never die of prostate cancer when the dose is escalated to 78 Gy or with hormonal treatment [4]. These accomplishments in outcome must be weighed against the complication rate. Fortunately, technology and parameters for dose restriction to normal tissues have provided measures to ensure that the therapeutic index remains high. In this document, we attempted to review the change in toxicity profiles from 2D radiation to the era of image-guided radiotherapy in the face of a dramatic increase in the number of older patients. We analyzed the changing trends in adverse effects of external beam radiotherapy (EBRT). Although there are many good outcomes of brachytherapy (BT) for localized prostate cancer, to keep the analysis simple we did not include BT.

**LITERATURE REVIEW**

From conventional (2D) radiotherapy to 3D conformal radiotherapy

Standard 2D planning techniques used until the 1990s with limited total doses of up to 70 Gy were expected to cause toxicity. In the 1990s, 3D planning techniques were developed, and 3D conformal radiation therapy (3D-CRT) was combined with computer software to integrate CT images of the patient's internal anatomy. These approaches allowed physicians to work with a high-dose irradiated volume. The role of dose escalation has been estimated in several randomized controlled trials, and the results indicate that a higher dose improves PSA control with elevated toxicity, mainly in the form of late radiation toxicity. Dearden et al. conducted a randomized trial to compare the toxicity of 2D with 3D-CRT with a standard dose of 64 Gy in daily 2-Gy fractions and concluded that conformal techniques significantly lower the risk of radiation-induced rectal toxicity when compared with the conventional fractionation schedule [5]. In the 253 men treated, significantly fewer men developed rectal bleeding in the conformal group than in the nonconformal group (5% vs 15%, P = 0.006; 5% vs 15%, RTOG Grade 2, P = 0.01). There were no differences between the groups with respect to the development of radiation-induced proctitis. However, the rates of late radiation-induced proctitis are significantly lower in the conformal group than in the nonconformal group (5% vs 15%, RTOG Grade 1, P = 0.006; 5% vs 15%, RTOG Grade 2, P = 0.01). There were no differences between the groups with respect to the development of radiation-induced proctitis. However, the rates of late radiation-induced proctitis are significantly lower in the conformal group than in the nonconformal group (5% vs 15%, RTOG Grade 1, P = 0.006; 5% vs 15%, RTOG Grade 2, P = 0.01). There were no differences between the groups with respect to the development of radiation-induced proctitis. However, the rates of late radiation-induced proctitis are significantly lower in the conformal group than in the nonconformal group (5% vs 15%, RTOG Grade 1, P = 0.006; 5% vs 15%, RTOG Grade 2, P = 0.01). There were no differences between the groups with respect to the development of radiation-induced proctitis. However, the rates of late radiation-induced proctitis are significantly lower in the conformal group than in the nonconformal group (5% vs 15%, RTOG Grade 1, P = 0.006; 5% vs 15%, RTOG Grade 2, P = 0.01). There were no differences between the groups with respect to the development of radiation-induced proctitis. However, the rates of late radiation-induced proctitis are significantly lower in the conformal group than in the nonconformal group (5% vs 15%, RTOG Grade 1, P = 0.006; 5% vs 15%, RTOG Grade 2, P = 0.01).
bladder function after treatment (53% vs 59% ≥ Grade 1, P = 0.34; 20% vs 23% ≥ Grade 2, P = 0.61). After a median follow-up period of 3.6 years, there was no significant difference between the groups in local tumor control.

Koper et al. reported that conformal radiotherapy at a dose level of 66 Gy does not significantly decrease the incidence of gastrointestinal (GI) rectal (10% vs 7%), anal and genitourinary (GU) bladder toxicity compared with conventional radiotherapy in a Phase 3 trial [6]. There is a significant relationship between acute and late toxicity and the anal volume exposed to 90% of the tumor dose. GI and GU symptoms at the start have a major impact on late toxicity.

Yoshioka et al. compared late toxicity for 2D- with 3D-CRT using uniform radiotherapy of 70 Gy in 35 fractions, employing the classical four-field technique with gantry angles of 0°, 90°, 180° and 270° in 362 patients at five institutions with a median follow-up of 4.5 years (range, 1.0–11.6) [7]. The 5-year overall and cause-specific survival rates were 93% and 96%, respectively. The mean ± SD of portal field size in the right–left, superior–inferior and anterior–posterior directions was 10.8 ± 1.1, 10.2 ± 1.0 and 8.8 ± 0.9 cm for a 2D simulation and 8.4 ± 1.2, 8.2 ± 1.0 and 7.7 ± 1.0 cm for a 3D simulation (P < 0.001), respectively. No Grade 4 or 5 late toxicity was observed. The actuarial 5-year Grade 2–3 GU and GI late toxicity rates were 6% and 14% respectively, whereas the corresponding late rectal bleeding rate was 23% for a 2D simulation and 7% for a 3D simulation (P < 0.001). The use of a CT simulation and the resultant reduction in portal field size were significantly associated with reduced late GI toxicity, and particularly with less rectal bleeding.

Consequently, several dose escalation studies have been conducted (Table 1) [8–16]. Viani et al. performed a meta-analysis of seven randomized controlled trials with a total patient population of 2812 [1]. Pooled results from these studies showed a significant reduction in the incidence of biochemical failure in patients with prostate cancer treated with high-dose radiotherapy (P < 0.0001). On the other hand, there was no difference in the mortality rate (P = 0.38) or in specific prostate cancer mortality rates (P = 0.45) between the groups receiving high-dose radiotherapy and conventional-dose radiotherapy. Nevertheless, there were more cases of late Grade ≥ 2 GI toxicity after high-dose radiotherapy than after conventional dose radiotherapy. In the subgroup analysis, patients classified as being at a low (P = 0.007), intermediate (P < 0.0001), and high risk (P < 0.0001) of biochemical failure all showed a benefit from high-dose radiation therapy.

From 3D-CRT to intensity-modulated radiotherapy
A further advancement in radiotherapy techniques that facilitates precise dose delivery is intensity-modulated radiation therapy (IMRT). This technique allows dose escalation while minimizing damage to the normal tissue (Table 2) [17–25]. Zelefsky et al. compared outcomes between 830 3D-CRT and 741 IMRT treatments and concluded that serious late toxicity is unusual, despite the delivery of high radiation doses from 66–81 Gy with a median follow-up of 10 years [17]. Higher doses were associated with increased GI and GU Grade 2 toxicity, but the risk of proctitis was significantly reduced with IMRT. Acute symptoms were a precursor of late toxicity in these patients. After 10 years, the actuarial likelihood of the development of ≥ Grade 2 GI toxicity was 9%. The use of IMRT significantly reduced the risk of GI toxicity compared with patients treated with conventional 3D-CRT (from 13% to 5%; P < 0.001). Among patients who experienced acute GI symptoms, the 10-year incidence of late toxicity was 42%, compared with 9% in those who did not experience acute symptoms (P < 0.0001). The 10-year incidence of late Grade ≥ 2 GU toxicity was 15%. Patients treated with 81 Gy IMRT had a 20% incidence of GU symptoms 10 years later, compared with 12% in patients treated with lower doses (P = 0.01). From the same institute, Spratt et al. reported results from a large cohort of 1002 patients treated with high-dose radiation of 86.4 Gy with a median follow-up period of 5.5 years (range, 1–14 years) [18]. A total of 587 patients (59%) were treated with neoadjuvant and concurrent androgen deprivation therapy (ADT). For low-, intermediate- and high-risk groups, 7-year biochemical relapse-free survival outcomes were 98.8%, 85.6% and 67.9%, respectively (P < 0.001). The incidence of actuarial 7-year Grade ≥ 2 late GI and GU toxicity was 4.4% and 21.1%, respectively. Late Grade 3 GI and GU toxicity was experienced by seven patients (0.7%) and 22 patients (2.2%), respectively.

Vora et al. reported an improved PSA control rate as a result of high-dose IMRT compared with conventional-dose 3D-CRT without elevated toxicity. A total of 416 patients with a minimum follow-up of 3 years (median 5 years) were included [18]. Of these, 271 patients received 3D-CRT with a median dose of 68.4 Gy (range, 66–71 Gy). Next, 145 patients received IMRT with a median dose of 75.6 Gy (range, 70.2–77.4 Gy). The 5-year biochemical control rate was 74.4% and 84.6% with 3D-RT and IMRT, respectively (P = 0.0326). The high-dose IMRT group experienced greater acute GI toxicity (P = 0.094) than the 3D-CRT group, but the difference was not statistically significant. There were no differences in acute GI (P = 0.83), chronic GU (P = 0.33), and chronic GI (P = 0.24) toxicity between the two groups.

Sharma et al. reported that IMRT + ADT reduced GI toxicity compared with 3D-CRT + ADT [19]. ADT has been shown to increase late Grade ≥ 2 rectal toxicity when used concurrently with 3D-CRT. A total of 293 men underwent 3D-CRT (n = 170) or IMRT (n = 123) with concurrent ADT (<6 months, n = 123; ≥6 months, n = 170). The median radiation dose was 76 Gy for 3D-CRT and 76 Gy for IMRT. Toxicity was assessed using a patient symptom questionnaire
Table 2. 3D conformal radiation therapy (3D-CRT) and intensity-modified radiation therapy (IMRT)

| Author (Institute) | Year (Pt No.) | Study | Follow-up period (median) | Radiotherapy | PSA control rate* (L/I/H) | Adverse toxicity criteria | Adverse reaction Late G2 or more if otherwise cited |
|-------------------|---------------|-------|---------------------------|--------------|---------------------------|-------------------------|----------------------------------------------------------------------------------|
| Zelefsky [17] (MSK) | 2008 (n = 1571) | 3D-CRT vs IMRT n = 830 vs 741 | 10 years | 3D-CRT vs IMRT 66-75.6 Gy vs 81 Gy | NA | CTCAE ver. 3.0 | GI 13% vs 5% 
   \( P \leq 0.001 \) 
   GU 20% vs 12% 
   \( P = 0.01 \) | IMRT reduces GI but increases GU toxicity \( \text{Acute related to late toxicity} \) |
| Vora [18] (Mayo)  | 2007 (n = 416) | 3D-CRT vs IMRT n = 271 vs 145 | 5 years | 3D-CRT vs IMRT 68.4 (66–71) Gy vs 75.6 (70.2–77.4) Gy | 74.4% vs 84.6% \( P = 0.032 \) | CTCAE ver. 4.0 | GI 16% vs 24% 
   GU 29% vs 22% | high dose IMRT improved PSA control in \( \text{intermediate and high risk groups} \) |
| Sharma [19] (Fox Chase) | 2011 (n = 293) | 3D-CRT + ADT vs IMRT + ADT n = 170 vs 123 | 86 months vs 40 months | NA | NA | Fox chase modified LENT | GI 20% vs 8% \( P \geq 0.01 \) 
   GU 6.5% vs 4.8% | IMRT reduced GI toxicity |
| Bekekman [20] (UPEN) | 2011 (n = 12 598) | 3D-CRT vs IMRT n = 6753 vs 5845 | 24 months | SEER–Medicare database | NA aged 65 years or older | NA | Medicare patient claim composite bowel complication | bowel 22.5% vs 18.8%; \( HR = 0.86 \) proctitis/hemorrhage; \( HR = 0.78 \) | IMRT slightly reduced GI toxicity |
| Sheets [21] (North Carolina) | 2012 (n = 12 976) | 3D-CRT vs IMRT (vs proton) n = 6753 vs 5845 vs 1368 | 44 months vs 64 months vs 50 months | SEER–Medicare database | NA (propensity score–adjusted analyses) | NA | Medicare patient claim | GI 14.7 vs 13.4 per 100 person-years 
   Hip fracture 1.0 vs 0.8, ED 5.3 vs 5.9 | IMRT less GI toxicity and hip fractures, more ED than 3D-CRT 
   (IMRT less GI toxicity than proton 12.2 vs 17.8) |
| Michalsky [22] (RTOG 0126) | 2013 (n = 748) | RCT; 3D-CRT vs IMRT n = 491 vs 257 | 4.6 years vs 3.5 years | 79.2 Gy | NA | CTC ver. 2.0 RTOG/EORTC | GI 22% vs 15.1% \( P = 0.039 \) 
   GU NA | IMRT reduced GI toxicity but not significant in multivariate analysis |
| Alicikus [23] (MSK) | 2011 (n = 170) | Long-term follow-up | 99 months | 81 Gy | 10 years \( 81%/78%/62\% \) | CTCAE ver. 3.0 | GI 3% 
   GU 16% | 99 months long-term results |
| Spratt [24] (MSK) | 2013 (n = 1 002) | High-dose IMRT | 5.5 years | 86.4 Gy | 7 years \( 99%/86%/68\% \) | CTCAE ver. 4.0 | GI 4.4% 
   GU 21.1% | 86.4 Gy feasible |

Continued
using a Fox Chase Modified Late Effect Normal Tissues (LENT) scale. The mean follow-up period was 86 months for the 3D-CRT group and 40 months for the IMRT group. The acute GI toxicity (odds ratio [OR], 4; 95% confidence interval [CI], 1.6–11.7; \( P = 0.005 \)) was significantly greater with 3D-CRT than with IMRT and was independent of the ADT duration (i.e., <6 vs ≥6 months). The time to development of late GI toxicity was significantly longer in the IMRT group. The 5-year estimated incidence of Grade ≥2 GI toxicity was 20% for 3D-CRT and 8% for IMRT (\( P = 0.01 \)). In multivariate analysis, Grade ≥2 late GI toxicity [hazard ratio (HR), 2.1; 95% CI, 1.1–4.3; \( P = 0.04 \)] was more prevalent among the 3D-CRT-treated patients.

Bekelman et al. conducted an observational cohort study using data on registry and administrative claims from the Surveillance, Epidemiology and End Results (SEER)–Medicare database for patients aged ≥65 years diagnosed with non-metastatic prostate cancer in the USA who received IMRT (\( n = 5845 \)) or CRT (\( n = 6753 \)) [20]. IMRT was associated with a reduction in composite bowel complications (24-month cumulative incidence 18.8% vs 22.5%; HR, 0.86; 95% CI, 0.79–0.93) and proctitis/hemorrhage (HR, 0.78; 95% CI, 0.64–0.95). IMRT use was not associated with higher rates of composite urinary complications (HR, 0.93; 95% CI, 0.83–1.04) or cystitis/hematuria (HR, 0.94; 95% CI, 0.83–1.07). The incidence of erectile dysfunction (ED) involving invasive procedures was low and did not differ significantly between the groups, although IMRT was associated with an increase in new diagnoses of ED (HR, 1.27; 95% CI, 1.14–1.42). Those authors concluded that IMRT is associated with a small reduction in composite bowel complications and proctitis/hemorrhage compared with CRT in elderly men with non-metastatic prostate cancer.

Sheets et al. reported that the use of IMRT vs CRT increased from 0.15% in 2000 to 95.9% in 2008 [21]. In propensity score-adjusted analysis (\( P = 12.976 \)), men who received IMRT vs CRT were less likely to receive a diagnosis of GI morbidity (absolute risk, 13.4 vs 14.7 per 100 person-years; relative risk [RR], 0.91; 95% CI, 0.86–0.96) or a hip fracture (absolute risk, 0.8 vs 1.0; RR, 0.78; 95% CI, 0.65–0.93), but more likely to receive a diagnosis of ED (absolute risk, 5.9 vs 5.3; RR, 1.12; 95% CI, 1.03–1.20).

Recently, Michalsky et al. reported preliminary toxicity analysis of 3D-CRT versus IMRT on the high-dose arm of the RTOG 0126 prostate cancer trial [22]. Of 763 patients randomized to the 79.2 Gy arm, 748 were eligible and evaluable: 491 and 257 were treated with 3D-CRT and IMRT, respectively. For both bladder and rectum, the volumes receiving 65, 70 and 75 Gy were significantly lower with IMRT (for all \( P < 0.0001 \)). For Grade ≥2 acute GI/GU toxicity, both univariate and multivariate analysis showed a statistically significant decrease in Grade ≥2 acute collective GI/GU toxicity for IMRT. There were no significant
differences between 3D-CRT and IMRT in acute or late Grade ≥2 or Grade ≥3 GU toxicity. In multivariate analysis, IMRT showed a 26% reduction in Grade ≥2 late GI toxicity (\(P = 0.099\)). Acute Grade ≥2 toxicity was associated with late Grade ≥3 toxicity (\(P = 0.005\)). RT modality was not significant, whereas white race (\(P = .001\)) and rectal V70 ≥15% were associated with G2+ rectal toxicity (\(P = 0.034\)). Thus, IMRT is associated with a significant reduction in acute Grade ≥2 GI/GU toxicity. There is a trend for a clinically meaningful reduction in late Grade ≥2 GI toxicity with IMRT. The occurrence of acute GI toxicity and large (>15%) volumes of rectum >70 Gy are associated with late rectal toxicity.

Ariskus et al. assessed long-term tumor control and toxicity outcomes after high-dose IMRT in 170 patients who received 81 Gy with a median follow-up period of 99 months [23]. The 10-year PSA control rates were 81% for the low-risk group, 78% for the intermediate-risk group, and 62% for the high-risk group. The 10-year cause-specific mortality rates were 0%, 3% and 14%, respectively. The 10-year likelihood of developing Grade 2 and 3 late GU toxicity was 11% and 5%, respectively; and the 10-year likelihood of developing Grade 2 and 3 late GI toxicity was 2% and 1%, respectively.

To our knowledge, only one manuscript dealt with the constraints of IMRT, but the data were not significant in multivariate analysis. Pederson et al. reported that a 4-year absence of maximal Grade ≥2 late toxicity is observed in 81% and 91% of patients in terms of GU and GI symptoms respectively, with a median follow-up period of 41 months after 76 Gy of IMRT [25]. In multivariate analysis, whole-pelvis IMRT was associated with Grade ≥2 GU toxicity, and age was associated with Grade ≥2 GI toxicity. The absence of Grade ≥2 GI toxicity after 4 years was observed in 100% of men with rectal V70 ≤10%, V65 ≤20% and V40 ≤40%; 92% of men with rectal V70 ≤20%, V65 ≤40% and V40 ≤80%; and 85% of men exceeding these criteria (\(P = 0.13\)). These criteria were more strongly associated with GI toxicity in men aged ≥70 years (\(P = 0.07\)). At present, no confirmed constraints exist in IMRT, and further studies are required.

**From IMRT to image-guided radiation therapy**

Image-guided radiation therapy (IGRT) is the process of frequent 2D and 3D imaging, in the course of a radiation treatment, intended to direct radiation therapy using imaging coordinates of the actual radiation treatment plan. This approach allows physicians to deliver accurate radiation therapy with a reduction in the set-up margin (Table 3) [26–31].

Zelefsky et al. reported outcomes of 86.4 Gy for 186 image-guided IMRT (IG-IMRT) treatments with a median follow-up period of 2.8 years using the placement of fiducial markers and daily tracking by kilovoltage imaging of target positioning [26]. This technique is associated with an improvement in biochemical tumor control among high-risk patients and a lower rate of late urinary toxicity compared with a similar dose of IMRT. This group of patients was retrospectively compared with a similar cohort of 190 patients without fiducial markers (non-IGRT). The 3-year likelihood of Grade ≥2 urinary toxicity for IGRT and non-IGRT cohort was 10.4% and 20.0%, respectively (\(P = 0.02\)). Multivariate analysis identifying predictors of Grade ≥2 late urinary toxicity demonstrated that in addition to the baseline International Prostate Symptom Score (IPSS), IGRT was associated with significantly less late urinary toxicity compared with the non-IGRT group. The incidence of Grade ≥2 rectal toxicity was low in both treatment groups (1.0% and 1.6%, respectively; \(P = 0.81\)). No differences in PSA relapse-free survival outcomes were observed in low- and intermediate-risk patients when either treated with IGRT or not treated with IGRT. Nonetheless, in high-risk patients, a significant improvement (97% vs 77.5%, \(P = 0.05\)) was observed 3 years after treatment with IGRT compared with non-IGRT.

Vargas et al. reported a Phase II adaptive radiation therapy (ART) trial in 331 patients with a median follow-up period of 1.6 years [27]. Low-risk patients (PSA <10, stage ≤T2a, Gleason score ≤7) received irradiation to the prostate alone (Group 1). All other patients, both intermediate and high risk, received irradiation to the prostate and seminal vesicles (Group 2). Grade 2 chronic rectal toxicity was experienced by 34 patients (10%; 9% experienced rectal bleeding, 6% proctitis, 3% diarrhea, and 1% rectal pain). Nine patients (3%) experienced Grade ≥3 chronic rectal toxicity (one Grade 4). The 2-year rates of Grade ≥2 and Grade ≥3 chronic rectal toxicity were 17% and 3%, respectively. No significant difference among dose levels was seen in the 2-year rate of Grade ≥2 chronic rectal toxicity. These rates were 27%, 15%, 14%, 17% and 24% for dose levels equal to or less than 72, 73.8, 75.6, 77.4 and 79.2 Gy, respectively (\(P = 0.3\)). Grade ≥2 chronic rectal bleeding was significantly greater in Group 2 than in Group 1, 17% vs 8% (\(P = 0.035\)).

Vora et al. reported [28] long-term disease control and chronic toxicity in 302 patients. Chronic toxicity was measured at the peak in symptoms and at the last visit. The median radiation dose delivered was 75.6 Gy (range, 70.2–77.4), and 35.4% of the patients received ADT. The patients were followed up until death or for 6–138 months (median, 91) for those alive at last evaluation. At last follow-up, only 0% and 0.7% of patients had persistent Grade ≥3 GI and GU toxicity, respectively.

Tomita et al. reported helical tomotherapy (HT) results for 241 patients with a median follow-up time of 35 months [29]. Late Grade 2–3 rectal toxicity was observed in 18 patients (7.4%). Age, the maximum dose for the rectum, V70 and V60 of the ≥ Grade 2 toxicity group were significantly higher than in the ≤ Grade 1 toxicity group (\(P = 0.000\,93, 0.048, 0.0030\) and 0.0021, respectively). None of the factors was significant.
### Table 3. Intensity modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT)

| Author (Institute) | Year (Pt No.) | Study IGRT methods | Follow-up period (median) | Radiotherapy | PSA control rate* (L/I/H) | Adverse toxicity criteria | Adverse reaction Late Grade 2 or more if otherwise cited |
|--------------------|---------------|-------------------|---------------------------|--------------|--------------------------|---------------------------|--------------------------------------------------|
| Zelefsky [26] (MSK) | 2012 (n = 376) | IMRT vs IG-IMRT CBCT, Fiducial \( n = 190 \text{ vs } 186 \) | 2.8 years | 86.4 Gy | High-risk group \( (n = 67 \text{ vs } 35) \) 3 years 77.7% vs 97% vs 97% \( P = 0.05 \) | CTCAE ver. 3.0 | GI 1.6% vs 1.1% GU 20% vs 10.4% \( P = 0.02 \) | IG-IMRT improved PSA control in high-risk group IGRT reduced urinary toxicity |
| Vargas [27] (William Beaumont) | 2005 (n = 331) | PII 63–79.2 Gy CBCT, Portal | 1.6 years | 3D-CRT 70.2 Gy vs 72 Gy vs 73.8 Gy vs 75.6 Gy vs 77.7 Gy vs 79.2 Gy | NA | CTCAE ver. 2.0 | GI 27% vs 21% vs 11% vs 8% vs 15% vs 18% #Group 2 vs Group 1, 17% vs 8% \( P = 0.035 \) | Acute related to late toxicity Wider field elevated toxicity |
| Vora [28] (Mayo) | 2013 (n = 302) | Long-term follow-up US or fiducial | 91 months | 75.6 Gy (70.2–77.4) | 9 years (77.4%/69.6%/53.3%) | CTCAE ver. 4.0 | GI 2.3% GU 10% | Long-term results |
| Tomita [29] (Aichi CC) | 2013 (n = 241) | Helical tomotherapy MVCT | 35 months | 74–78 Gy | NA | RTOG | GI 7.4% | |
| Eade [31] (Australia) | 2013 (n = 101) | Dose escalation Fiducial and/or daily CBCT | 21 months | 78.3–84 Gy | NA | CTCAE ver. 3.0/IPSS | GI 2% GU 3% | >78 Gy IG-IMRT well tolerated |

IG-IMRT = image guided IMRT, MSK = Memorial Sloan-Kettering Cancer Center, Aichi CC = Aichi Cancer Center Hospital, US = ultrasonography, CBCT = cone-beam computed tomography, NA = not available, CTCAE = Common Terminology Criteria for Adverse Events, RTOG = Radiation Therapy Oncology Group, IPSS = International Prostate Symptom Score, GI = gastrointestinal, GU = genitourinary, *5 years unless otherwise stated, L/I/H = low risk/intermediate risk/high risk groups, \( n = 11 \text{ vs } 48 \text{ vs } 28 \text{ vs } 136 \text{ vs } 75 \text{ vs } 33 \), #Low risk group was treated for prostate only (Group 1) and other treated for seminal vesicle and prostate (Group 2).
in multivariate analysis. Nishimura et al. also examined late toxicity after HT in 117 patients [30] and found 7.7% cases of GI toxicity ≥ Grade 2 and 6.8% cases of GU toxicity ≥ Grade 2. They noted that these figures were higher than expected for IGRT–IMRT. These reports imply that the advanced IGRT techniques do not always lead to a reduction in late toxicity. Eade et al. used rectal dose constraints V65 < 17% and V40 < 35% [31]. The bladder dose goals were V65 < 25% to 25% and V75 < 5% for IGRT–IMRT. These reports imply that the advanced IGRT techniques do not always lead to a reduction in late toxicity. In other words, reducing V75 by only 5% (from 15% to 10%) has a significant impact on the complication probability, whereas reducing V50 from 50% to 45% makes relatively little difference for rectal bleeding [61]. Several authors proposed custom-made constraints based on generic and patient-specific risk factors. For example, an Italian group attempted to examine the influence of a prior abdominal surgical operation on the correlation of G2–G3 bleeding with a cholecystectomy [OR = 6.5, P = 0.002] and on a secondary correlation with an appendectomy (OR = 2.7, P = 0.10) [39, 59]. Next, [36, 51, 66] they proposed a modified constraint for bleeding V70 < 15% (V75 < 5%) for patients with a history of abdominal or pelvic surgical procedures, but V70 < 25% (V75 < 15–20%) otherwise.

(ii) GI incontinence According to Denham et al. [53], fecal urgency and bleeding have the highest impact on daily life (Table 4) [37–77]. Koper et al. [6] have shown that patients are more bothered by symptoms such as soiling, fecal loss, and mucus discharge rather than blood loss, urges, and bowel cramps. Reported risk factors for late incontinence are: a previous abdominal or pelvic surgical procedure [37, 38, 40, 69], diabetes mellitus [40], a history of cardiac problems [40], the use of antihypertensive drugs (a protective factor) [40, 69], prior or acute symptoms (mucous discharge, proctitis) [44, 72], hemorrhoids [66], seminal vesicle irradiation [72], and previous bowel disease [69].

Potential mechanisms involved in the development of incontinence could be the reduced absorption capacity of the rectal mucosa, which may be expected to have a large volume effect as well as neurovascular damage impairing the musculature surrounding the rectum. Several recent studies produced evidence of dose–volume relations for late rectal incontinence [36–38]. It was demonstrated recently that a DVH constraint of rectum V40 < 65% or V40 < 80% (or a mean rectal dose of < 45–50 Gy) reduces the risk of late incontinence [6, 18, 20, 36–38, 58, 59, 61–63, 66–71]. Although late incontinence is quite a rare side-effect in modern radiotherapy, the application of this constraint has the potential to reduce the risk to < 2%. In addition, several authors found a link to acute adverse reactions of Grade 2 and 3, which correlates strongly with the mean dose; these data suggest that the reduction of the dose bath delivered to the whole rectum may have an impact on the risk of acute toxicity [37, 38, 74]. Detailed analysis of the subarea DVH could provide further insights into the incontinence risks [33, 38, 63, 73]. Heemsbergen et al. reported a subarea difference:
for bleeding and a mucus loss, the strongest correlation was found for the dose delivered to the upper 70–80% of the ano-rectal region \( (P < 0.01) \) [73]. For soiling and fecal incontinence, they found the strongest association with the dose delivered to the lower 40–50% of the anal canal [38]; 53 Gy delivered to the anal surface was found to be an important constraint [75]. Al-Abany et al. also reported dose constraints: a dose \( V35 < 60\% \) or \( V40 < 40\% \) of the anal sphincter region volume for fecal leakage [76]. A recent study proposed more detailed dose constraints: 30 Gy delivered to the internal anal surface, 10 Gy to the external anal surface, 50 Gy to the puborectalis muscle, and 40 Gy to the levator ani muscles [68]. Nevertheless, the prevalence and severity of diarrhea and rectal bleeding after 3D-CRT have been reported to be reduced in the long run compared with 2D RT [5–16]. Yeoh et al. showed that urgency of defecation, the most frequent sequela of RT, is not improved by the 3D-CRT technique, and is more frequent compared with the 2D technique [77]. They compared the frequency of anomalies between 3D-CRT and 2D radiotherapy 2 years after treatment: increased

| Table 4. Reported risk factors for adverse reaction |
|-------------------------------------------------|
| **Risk factors for late gastrointestinal (GI) symptom** |
| (1) Rectal bleeding |
| Hypertension [32], Increased age [32, 33], Large rectum volume [34, 35] |
| Abdominal surgery [36–40], Acute symptom [17, 37–39, 43, 46–53], Cardiac history [40] |
| Androgen deprivation therapy (ADT) [41–45], Hemorrhoids [54, 55], Diabetes Mellitus [56–59] |
| Inflammatory bowel disease [60] |
| **DVH (rectum)** |
| \( V50 < 45–55\% \), \( V60 < 35–40\% \), \( V65 < 20–25\% \), \( V70 < 15–25\% \), \( V75 < 5–15\% \) \[15, 22, 36, 40, 45, 46, 50, 51, 53, 56, 59–65\] |
| \( V40–60 \) Gy would be also important if prescribed \( 78 \) Gy or more \[2, 36, 46, 51, 55, 59–68\] |
| QUANTEC: \( V50 < 50\% \), \( V60 < 35\% \), \( V65 < 25\% \), \( V70 < 20\% \), \( V75 < 15\% \) \( \Rightarrow \) Grade 2 < 15% [61] |
| \( *n = 0.09 \) (95% CI: 0.04–0.14); \( m = 0.13 \) (0.10–0.17); TD50 = 76.9 (73.7–80.1) Gy [61] |
| (2) Incontinence |
| Abdominal surgery [37, 38, 40, 69], Diabetes Mellitus [40], Cardiac history [40] |
| Antihypertensive drug (protective factor) [40, 69], Acute or prior (including mucous discharge, proctitis) [40, 72, 73] |
| Hemorrhoids [66], seminal vesicle irradiation [72], Previous bowel disease [69] |
| **DVH (Anorectal–anal canal)** |
| Anorectal \( V40 < 65–80\% \) [37, 38], Mean dose < 45–50 Gy [6, 18, 36–38, 58, 59, 61–63, 66–71] |
| Anal canal <37 Gy [73–75], Anal sphincter lesion \( V35 < 60\% \) \( V40 < 40\% \) [76] |
| **Risk factors for late genitourinary (GU) symptom** |
| ADT [37, 38], TURP [38], Hypertension [38], Pre-RT symptom [38] |
| Acute symptom [17, 43], Increased age [82], Pre-RT GU medication [47] |
| **DVH (Bladder)** |
| Max dose <78 Gy to 80 Gy [17, 54, 80] \( V30 < 30 \) cm\(^3\), \( V82 < 7 \) cm\(^3\) [80] |
| QUANTEC: \( V65 \leq 50\% \), \( V70 \leq 35\% \), \( V75 \leq 25\% \), \( V80 \leq 15\% \) RTOG 0415 recommendation [81] |
| Risk factors for erectile dysfunction (ED) |
| Pre-RT sexual function [23, 82], Increased age [47, 83, 87], Diabetes Mellitus [47, 87], ADT [47, 83, 87], Pre-RT PSA value [83] |
| **DVH (Penile bulb)** |
| \( V40 < 40\% \) \( V50 < 20\% \) [84], Median >52.5 Gy [85], \( V70 < 70\% \) [88] |
| QUANTEC: Mean 95% 95% < 50 Gy, \( D60–70 < 70 \) Gy, \( D90 < 50 \) Gy \( \Rightarrow \) severe ED < 35% [88] |

*Lyman–Kutcher–Burman normal tissue complication probability model, DVH = dose–volume histogram, QUANTEC = quantitative analysis of effects on normal tissue in the clinic.
stool frequency (55% vs 53%, P = not significant (n.s.)), urgency of defecation (72% vs 47%, P < 0.05), fecal incontinence (28% vs 26%, P = n.s.), and rectal bleeding (38% vs 42%, P = n.s.). In the IMRT era, we are awaiting the evidence of reduction of those figures by IMRT or more modern techniques.

**Genitourinary adverse reactions**

Mild acute irritative urinary symptoms have been reported in several studies, whereas total urinary incontinence and other severe late urinary symptoms (i.e. urethral stricture) are rare.

ADT [37, 38], prior transurethral resection of the prostate (TURP) [38], hypertension [38], pretreatment GU complaints [38], the presence of acute GU toxicity [17, 43], age > 70 [82], and GU medications before IMRT [47] are risk factors of long-term urinary morbidity (Table 4) [37–38, 43, 47, 54, 70, 80–82].

In the case of the bladder, there is a clear dose effect when the whole organ is irradiated (i.e. for cystitis) [78]. On the other hand, in the case of prostate irradiation, the cranial portion of the bladder is generally spared, whereas the bladder neck and urethra are irradiated near the prescribed dose [80]. The lack of knowledge about the dose–volume modeling of bladder toxicity probably reflects the difficulties with accurate assessment of the amount of bladder wall that receives a certain dose. This is because large variations are observed in the bladder shape during treatment because of variable filling. Serial behavior was reported recently for late mild to severe toxicity [54], whereas serial–parallel behavior was reported for chronic moderate or severe urinary toxicity [80]. Both studies indicated that the fraction of bladder receiving >78–81 Gy is most predictive of late GU toxicity [17, 54, 80].

**Erectile dysfunction**

ED is not an immediate side-effect of RT (Table 4) [23, 47, 80–90], and the occurrence of spontaneous erection before treatment (Table 4) [23, 47, 81–90] is the best predictor of preservation of erectile function sufficient for intercourse [81–83]. Other clinical predisposing factors are older age [47, 82], diabetes mellitus [47, 82], ADT [82, 83] and previous PSA level [83]. Most, but not all, studies find an association between ED and dosimetric parameters [83–88]. Wernicke et al. reported significant constraints of V50 < 20% and V40 < 40%, and median D30, D45, D60 and D75 [84]. Roach et al. reported that patients whose median penile bulb dose was >52.5 Gy had a greater risk of ED based on the RTOG 9406 trial data [85]. They updated those constraints in quantitative analysis of effects on normal tissue in the clinic (QUANTEC) to a mean dose of V95 < 50 Gy, D60–70 < 70 Gy and D90 < 50 Gy [88] and recommend the use of the International Index of Erectile Function (IIEF) [88, 90]. The target organ at risk is not likely to be the penile bulb but appears to be a surrogate for yet to be determined structure(s) necessary for erectile function [87, 88], such as the crura, vascular structures, or other penile components [89]. Coverage of the planned target volume should not be compromised, and the use of magnetic resonance imaging (MRI) is preferable to define the apex of the prostate, with consequent efficient sparing of the organs at risk [82–86, 89].

**DISCUSSION**

There are many modalities in radiation therapy, which cause a range of incidences of late GI toxicity. Kim et al. analyzed 28 088 patients using the SEER data. The most common GI toxicity is GI bleeding or ulceration. GI toxicity rates are 9.3 per 1000 person-years after 3D-CRT, 8.9 per 1000 person-years after IMRT, 20.1 per 1000 person-years after proton therapy, and 2.1 per 1000 person-years for patients receiving conservative management. Radiation therapy is the most significant factor associated with an increased risk of GI toxicity (HR, 4.74; 95% CI, 3.97–5.66). Even after 5 years, the radiation group continues to experience significantly higher rates of new GI toxicity than the conservative management group (HR, 3.01; 95% CI, 2.06–4.39) [91].

The RTOG or CTCAE scoring system has been widely used for assessment of toxicity but not enough to meet the requirements, according to a recent radiotherapy outcome survey. This is because in these scoring systems, compliance-related symptoms (such as stool frequency) and proctitis-related symptoms (such as rectal bleeding) are combined into one overall score. This feature may result in a loss of information and may obscure the relation between dose–volume parameters and complications [43]. Accordingly, several trials added a patient self-assessment questionnaire to obtain detailed information on morbidity. In addition, longitudinal assessment may add more useful information than peak score analysis can [43, 63, 68]. Guilford et al. found that endpoint—stool frequency—statistically significant dose–volume constraints are only derived by a longitudinal definition of toxicity in the outcome analysis of the MRC RT01 trial [63]. By the same token, an apparent association exists between acute side-effects experienced during the course of radiotherapy and the development of late toxicity. Heemsbergen et al. noted such an association between acute and late GI toxicity and postulated that late effects are a direct consequence of the initial tissue injury, which is reflected in acute symptoms resulting from inflammation of normal tissue [77]. According to their report, the presence of diarrhea during treatment is associated with a higher risk of late Grade ≥2 toxicity in late proctitis. They found that acute toxicity during treatment often manifests as tenesmus and internal hemorrhoid inflammation, which are associated with a higher likelihood of late proctitis. In addition, acute urinary symptoms that manifest during radiotherapy are linked to an increased risk of late Grade 2 urinary adverse events. Kim et al. [92] reported the long-lasting nature of GU toxicity: Grade 2–4 GU toxicity attributable to radiation therapy persists 10 years after treatment and thereafter based on comparison of
Incidence of metastasis (HR, 0.72 [95% CI, 0.63–0.83], P < 0.0001) and prostate cancer-specific death (HR, 0.78 [95% CI, 0.66–0.92], P < 0.0001). Although the biological underpinnings of this finding remain unknown, stratification by age in future trials is warranted. Several reports show that adverse reactions occur more frequently in older patients [32, 33, 77]. In this context, major data provided by a clinical trial (i.e., a large randomized controlled trial) were based on the data from patients younger than 80 years of age.

There are several limitations to our study. First, we did not analyze BT (although there are plenty of data in the literature) because we focused on the changes in adverse effects as a result of the advancement of EBRT from 2D to IMRT and IGRT. Second, as a result of this we did not analyze particle therapy because of the limited use of this therapy (both proton and carbon ion) in patients with prostate cancer except for clinical studies. Finally, hypofractionated radiotherapy was also excluded from this analysis, even though there is a hypothesis that hypofractionation has a radiobiological advantage in prostate carcinoma because of the low α/β ratio. This topic—the influence of fractionation—is beyond the scope of this study and will be explored in future studies.

In conclusion, the focus of toxicity analysis following radiotherapy for prostate cancer patients is changing from rectal bleeding to total elaborate QOL assessment.

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