Table 1 Estimated change due to radiation

Skeletal regions	FDG		NaF	
	Ratio before/after (day 2) radiation	95 % CI	Ratio before/after (day 3) radiation	95 % CI
Skull	0.57	0.44–0.72	1.9[c]	1.0–3.6
Mandible	0.53	0.42–0.68	1.9[c]	1.0–3.6
Humerus	0.51	0.40–0.65	2.3	1.2–4.3
Cervical	0.45	0.35–0.57	2.2	1.2–4.2
Thoracic	0.63[b]	0.49–0.80	2.2	1.2–4.2
Lumbar	0.55	0.43–0.71	2.4[d]	1.3–4.5
Femur[a]	0.46	0.36–0.59	2.4[d]	1.3–4.5
Tibia[a]	0.32[b]	0.25–0.42	2.4[d]	1.3–4.5
Overall average	0.50	0.41–0.60	2.2	1.1–4.5
Radiation effect to whole skeleton	< 0.0001		0.0314	
Radiation × skeletal region interaction	0.0002		0.0003	

FDG averaged over all regions is expected to decrease to 50 % of its pre-radiation level. This effect varied by region and was particularly low for the tibia, where post-radiation FDG was 32 % of its pre-radiation level. The NaF level averaged over all regions is expected to increase by a factor of 2.2 following radiation. However, this increase varied by region, from a factor of 1.9 in the skull and mandible to a factor of 2.4 in the femur and tibia. The wide confidence intervals are the result of variable effects seen in different mice (see Fig. 3c)

[a] Irradiated region

Model contrasts:

[b] For FDG, thoracic spine had a higher ratio and tibia had a lower ratio compared to the overall average ($p < 0.01$)

[c] For NaF, mandible and skull had a lower ratio compared to the overall average ($p < 0.01$)

[d] For NaF, lumbar spine, femur, and tibia had a marginally higher ratio compared to the overall average ($p < 0.1$)

significantly reduced FDG uptake at 32 % of pre-radiation levels. Thoracic vertebrae were higher and tibia was lower compared with an overall average reduction ($p < 0.01$, Table 1). Figure 3a shows FDG uptake averaged over all bone regions, demonstrating that radiation decreased FDG uptake overall ($p < 0.0001$) on day 2 after radiation. Despite individual variability, uptake after radiation was approximately 50 % of pre-radiation levels (Table 1). Figure 3b shows the difference in FDG uptake of individual mice before and after radiation. All mice showed a similar response pattern, with high activity in the skull and spine but large variations (coefficient of variation) between individuals. In contrast, radiation significantly suppressed metabolic activity in the entire skeleton in all subjects, with minimal individual variation.

Red bars in Fig. 2f show NaF uptake following radiation. In individual mice, the NaF uptake averaged over all regions increased by a factor of 2.2. The degree of uptake after radiation differed among the regions ($p = 0.0003$, Table 1). The skull and mandible exhibited less variation from the averaged value ($p < 0.01$, Table 1). The lumbar spine and the irradiated regions (i.e., femur and tibia) appeared to have higher variation ($p < 0.1$, Table 1). NaF uptake significantly increased among all the regions on day 3 after radiation ($p = 0.0314$, Fig. 3c). Individual variation in NaF uptake was greater than for FDG. Three mice exhibited large increases (>2.0), two mice had moderate

increases, and one slightly decreased. The uptake trend was similar before and after radiation (Fig. 3d).

Systemic Inflammatory Reaction

Radiation significantly reduced serum IGF-1 (Fig. 4, $p < 0.01$). IL-6 ($p = 0.06$) showed a trend for increases after radiation, while there were no statistically significant differences in TNFα, IFNγ, IL-10, and CXCL1. Statistical calculation of IL-12p70 and IL-1β could not be performed because most of the measurements were below the detection limit of the assay.
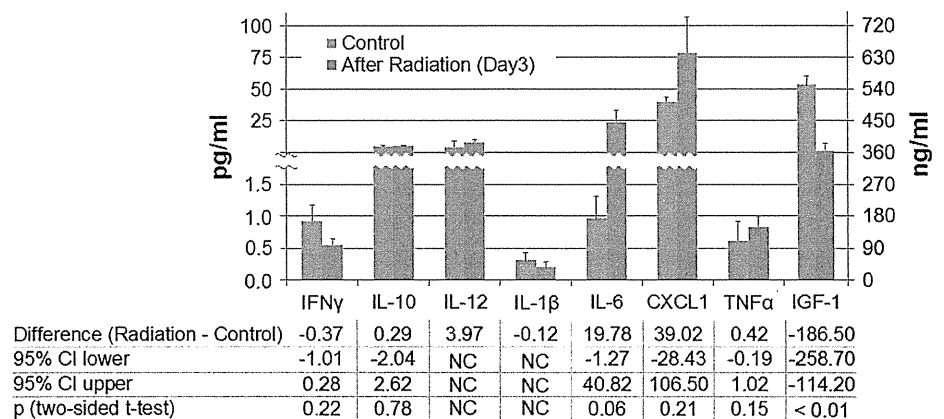
Discussion

Longitudinal non-invasive functional imaging with dual-radioisotope micro-PET/CT following local irradiation in BALB/c mice revealed regional heterogeneity in marrow and bone metabolic function. Regional changes in marrow metabolic and mineral remodeling with a concurrent abscopal effect early following radiation at a variety of sites were observed longitudinally. This is the first report to characterize functional heterogeneity and changes from medically relevant radiation exposure in the whole skeleton. The application of dual-radioisotope strategies allowed monitoring both local and distant effects on the entire
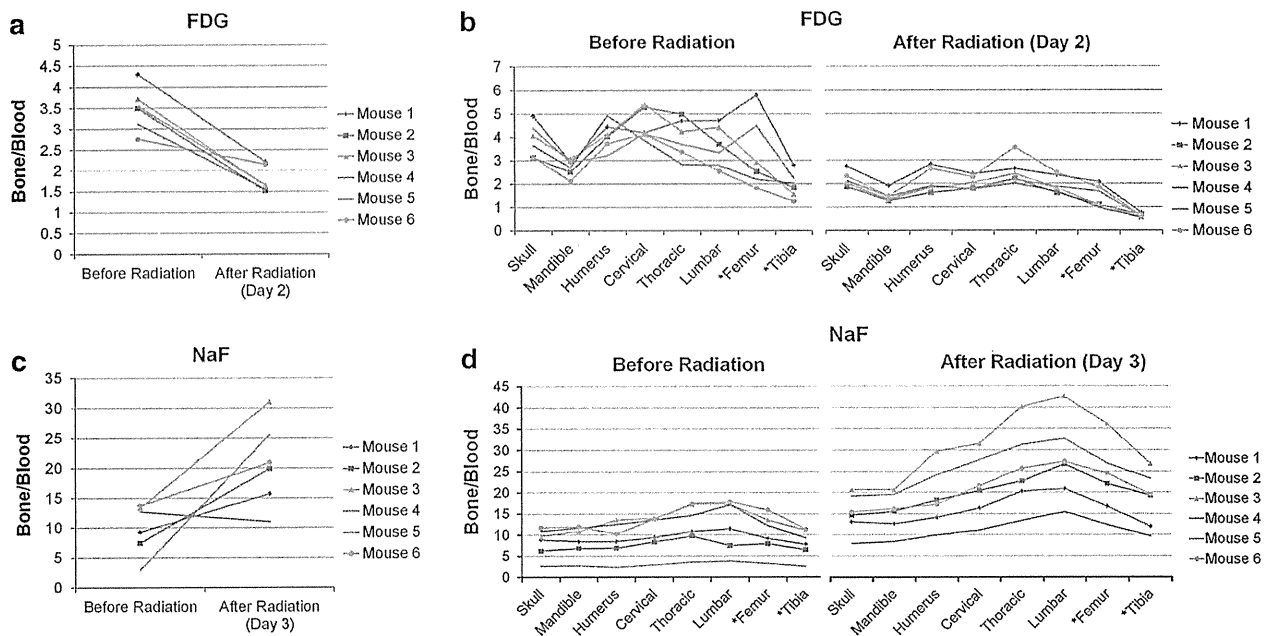
Fig. 3 Radiation response pattern on individual mouse marrow and bone metabolism. a Radiation decreases FDG uptake over all regions ($p < 0.0001$) on day 2 after radiation. b FDG uptake before and after radiation among eight different bone regions. c Radiation significantly increased NaF uptake among all the regions on day 3 after radiation ($p = 0.0314$). d NaF uptake before and after radiation among the bony regions. Star indicates irradiated bony region

Fig. 4 Systemic production of inflammatory mediators. The radiation group had lower mean IGF-1 and higher mean IL-6. *Right axis* for IGF-1. *NC* not calculated

	IFNγ	IL-10	IL-12	IL-1β	IL-6	CXCL1	TNFα	IGF-1
Difference (Radiation - Control)	-0.37	0.29	3.97	-0.12	19.78	39.02	0.42	-186.50
95% CI lower	-1.01	-2.04	NC	NC	-1.27	-28.43	-0.19	-258.70
95% CI upper	0.28	2.62	NC	NC	40.82	106.50	1.02	-114.20
p (two-sided t-test)	0.22	0.78	NC	NC	0.06	0.21	0.15	< 0.01

skeleton following targeted radiation, including the simultaneous functional assessment of two distinct but interdependent tissue compartments (i.e., marrow and bone). This technique may permit investigations into the multifactorial communication pathways between the two active tissue components in skeletal metabolism.

A previous study with clinical PET showed that FDG can identify hematologically active bone marrow at specific sites [17]; another investigation, employing NaF, demonstrated differences in bone metabolism in two regions following treatment [2]. These reports, however, investigated only limited skeletal regions. Heterogeneity in bone uptake by FDG and NaF indicates functional

differentiation among skeletal regions, suggesting metabolic differences at distinct bone sites. This heterogeneity could be due to structural and functional differences [18, 19]. A greater trabecular network and less marrow volume in the spinal bones may lead to greater cross-sectional area with a consequently higher metabolic activity. Previous studies have demonstrated site-specific molecular regulation involving the coordination of multiple genes [19], mirroring the developmental origin of each bone in the skeleton (i.e., "epigenetic postcode") [20]. This has been previously demonstrated for calvarial osteoblasts when compared to appendicular trabecular osteoblasts. Understanding regional functional differences in the skeleton

may therefore be crucial for (1) mapping sections of the skeleton to identify the regions that are most affected by disease or clinical intervention rather than random selection of skeletal regions to assay, (2) beginning to understand the role that local and whole-body skeletal environments may play while interacting with systemic endocrine and immune elements, and (3) developing treatment plans and evaluating the resulting response to disease management that incorporate factors such skeletal site and bone marrow composition.

FDG and NaF uptake of the irradiated region was significantly affected by treatment in the current investigation. Radiation decreased FDG uptake, likely indicating decreased bone marrow metabolism since the absolute number of bone marrow cells and their activity may affect FDG uptake [12]. This is in conformity with our previous report of a significant reduction in bone marrow cellularity by day 3 after radiation [9]. The early increase in NaF uptake after radiation was concomitant with a significant increase in marrow sinusoid and endosteal lining cells, which are ultimately responsible for appositional bone formation to the endosteum, in the skeleton employing a related experimental model [9]. Endosteal lining cells, i.e., committed quiescent osteoblasts, communicate with and are precursors to the osteocyte population embedded within the mineralized matrix. These cells likely regulate the influx and efflux of mineral ions and proteins into and out of the bone extracellular space, thereby serving as a kind of blood-bone barrier/interface [21]. Increases following radiation would then elevate NaF uptake in conjunction with increases in blood volume and interstitial fluids. While committed pre-osteoblasts respond to radiation damage by increased osteocalcin synthesis, the more pluripotent mesenchymal stem cell (MSC) population within the marrow space may respond to radiation damage by differentiating into adipocytes. We have observed some evidence of this indicated by increased peroxisome proliferator-activated receptor gamma gene expression in whole bone marrow following radiation (data not shown). This could explain the consistently observed increase in marrow adiposity after day 5 in mice exposed to sublethal doses of radiation or following a localized radiation exposure. Alternatively, radiation may induce cellular senescence in bone lining cells, thereby leading to a secretory phenotype (including IL-6 and TNFα) that could alter MSC lineage allocation.

Radiation may also lead to long-term impairment in skeletal structure and function. Our previously reported study found diminished bone structure in long-term follow-up after radiation [7]. Furthermore, there are likely biochemical and physical interactions between the bone surface (namely quiescent osteoblasts) and the adjacent marrow which may influence the radiation effects [22]. Dual-radioisotope micro-PET/CT could be a tool to develop a comprehensive understanding of radiation-induced effects on skeletal metabolism by investigating the temporal (short- and long-term) and spatial (local vs. distant) effects of radiation on bone structure and function.

An abscopal effect could result from immune system activation via cytokines elevated by radiation [23]. Irradiation to the abdomen of mice resulted in a suppression of bone marrow with increased synthesis of reactive oxygen species (ROS) in the shielded femur [24]. This observation may relate to the observed decreased FDG uptake to the non-irradiated sites. Increased vascular permeability in the non-irradiated region has also been reported [25]. Altered cytokine synthesis may therefore provide a potential mechanism explaining the early increase in NaF uptake in non-irradiated regions since IL-6 increases vascular permeability [26]. Significant increases in serum CXCL1 have been observed on day 3 after radiation [27]. This peptide is known to activate neutrophil populations and may contribute to increases in ROS [28] and vascular permeability [29]. Investigating focused radiation-induced changes at distant skeletal regions would facilitate an understanding of plausible microenvironmental changes in bone, which would be favorable for potential distant bone metastases [30, 31].

A potential mechanism for the radiation effect on both the osteoblast and osteoclast populations in local and distant sites is described in Fig. 5. Local radiation induces inflammation in irradiated bone by activating phagocytes. ROS directly generated by radiation, and secondarily by IL-6 and neutrophils, may be partly responsible for marrow damage. IL-6, CXCL1, and ROS can cause vascular permeability, thereby altering the movement of intercellular fluids. IGF-1, IL-6, and ROS may induce bone resorption via the activation of osteoclasts [32–34]. In our study we found higher IL-6 levels post-radiation, although we also observed diminished serum IGF-1 levels. These changes may lead to greater bone resorption and impaired bone formation, a recipe for significant bone loss in the irradiated area [7, 9, 35] and at non-irradiated skeletal sites [3]. As noted, radiation may also enhance the commitment of stromal marrow (i.e., pluripotent MSCs) to adipocyte differentiation and thus reduce long-term osteogenic potential [9].

There are challenges to performing longitudinal studies in a preclinical model. Repeated scans of the same animal impact anesthetic tolerance. Careful management of anesthetic delivery and the plane of anesthesia are essential steps to maintain data integrity. Damage to the tail vein due to repeated injections should be avoided by varying injection sites. Single-time point evaluations and radiation doses may have demonstrated a small set of cytokines that are activated after radiation. Further studies with additional time points and radiation doses will clarify the role of other pro- and anti-inflammatory cytokines in skeletal damage.
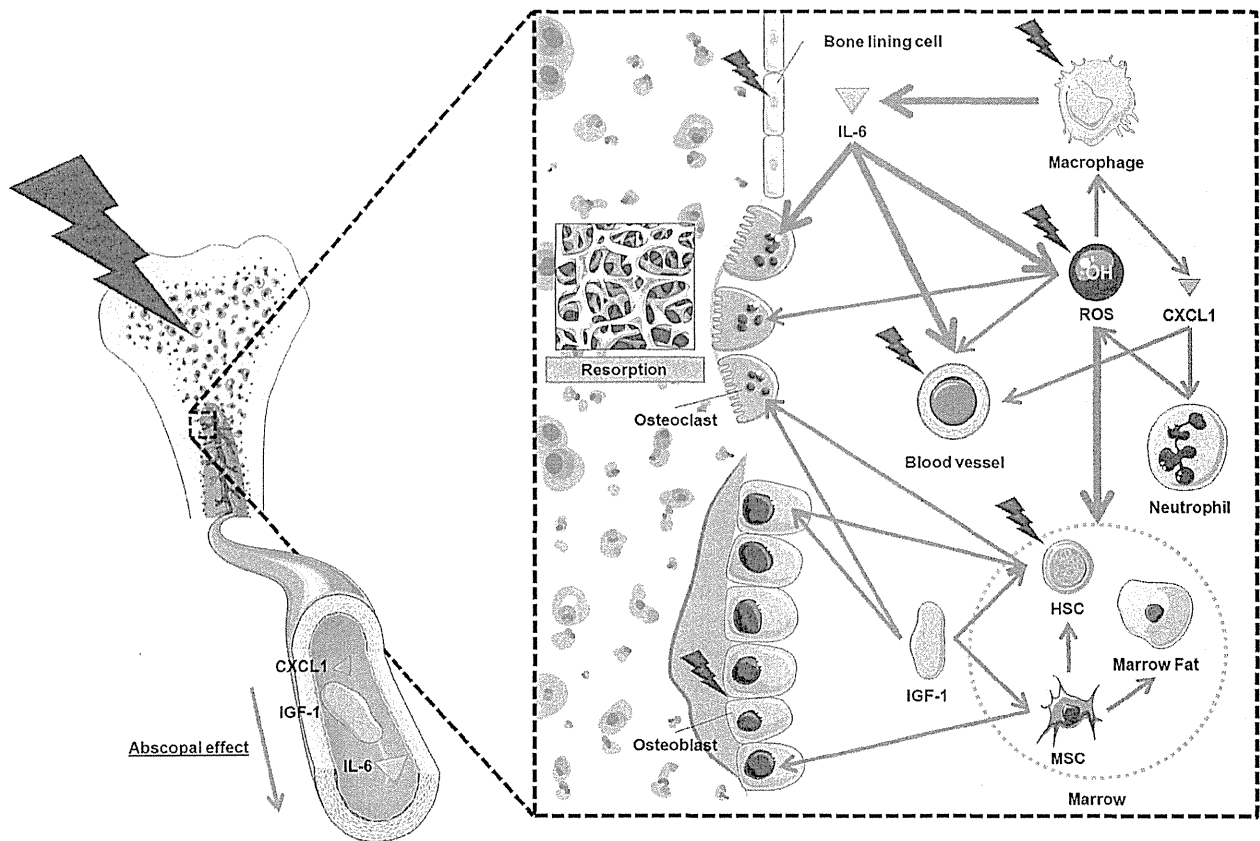
Fig. 5 Postulated mechanisms of local and systemic damage on marrow and bone in local radiation in an early time period. Bold arrows indicate greater effect caused by source. *HSC* hematopoietic stem cell, *MSC* mesenchymal stem cell, *ROS* reactive oxygen species, *IGF-1* insulin-like growth factor 1, *CXCL1* chemokine (C-X-C motif) ligand 1

Conclusions

Non-invasive longitudinal imaging with dual-radioisotope micro-PET/CT is feasible and allows the investigation of simultaneous changes in marrow and bone metabolic function. This technique may be useful for monitoring local and distal skeletal sites in response to radiation injury. There appears to be some functional skeletal heterogeneity among marrow and bone tissues. We observed temporally-related longitudinal changes in marrow metabolic and mineral remodeling locally and abscopally in response to local radiation injury. Molecular and biochemical mechanisms will be further investigated.

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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 ≥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	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% $P = 0.0007$	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

Michalsky [15] (RTOG 9406)	2010 (n = 1084)	Dose escalation n = 112 vs 300 vs 167 vs 256 vs 220	6.1–12.1 years	68.4 Gy vs 73.8 Gy vs 79.2 Gy vs 78 Gy	NA	RTOG	GI: 9% vs 7% vs 11% vs 10% vs 25% (#Group 1) $P = 0.0001$; GI 13% vs 9% vs 14% vs 16% vs 26% (#Group 2) $P = 0.0063$; GU 16–29%	Higher dose elevated GI toxicity
Beckendorf [16] (France)	2011 (n = 306)	RCT: GETUG n = 153 each	61 months	70 Gy vs 80 Gy	61% vs 72% $P = 0.03$	RTOG modified	GI 14% vs 19.5%; GU 10% vs 17.5% $P = 0.046$	higher dose improved PSA control with elevated urinary toxicity

MDAC = MD Anderson Cancer Center, MGH = Massachusetts General Hospital, MSK = Memorial Sloan-Kettering Cancer Center, 2D = conventional radiotherapy, NA = not available, RCT = randomized controlled trial, CTCAE = Common Terminology Criteria for Adverse Events, RTOG = Radiation Therapy Oncology Group, EORTC = European Organization for Research and Treatment of Cancer late morbidity, LENT/SOMA = Late Effect Normal Tissues/Subjective, Objective, Management, and Analytic, L/I/H = low risk/intermediate risk/high risk groups, GI = gastrointestinal, GU = genitourinary *5 years unless otherwise stated, #Group 1 treated for prostate only and Group 2 for seminal vesicle and prostate.

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. The PubMed database was searched for relevant articles published after 1990. We included only studies published in English assessing adverse effects in patients following curative EBRT that had large sample sizes (more than 100 patients) and/or important findings.

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 rectal bleeding [1, 2, 5–16] (Table 1). Most of the evidence of late radiation toxicity comes from those 3D-CRT dose escalation studies.

Dearnaley et al. conducted a randomized controlled 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 late radiation-induced proctitis after radiotherapy for prostate cancer [5]. In the 225 men treated, significantly fewer men developed radiation-induced proctitis and bleeding in the conformal group than in the conventional group (37% vs 56% ≥ Radiation Therapy Oncology Group (RTOG) Grade 1, $P = 0.004$; 5% vs 15% RTOG ≥ Grade 2, $P = 0.01$). There were no differences between the groups with respect to

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 GU 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	
3D-CRT vs IMRT								
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% $P \le 0.001$ GU 20% vs 12% $P = 0.01$	IMRT reduces GI but increases GU toxicity 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% $P = 0.032\,6$	CTCAE ver. 4.0	GI 16% vs 24% GU 29% vs 22%	high dose IMRT improved PSA control in 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	Fox chase modified LENT	GI 20% vs 8% $P = 0.01$ 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 and 46 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
IMRT								
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

Table 2. *Continued*

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	
Pederson [25] (Chicago)	2012 (n = 296)	Dose constraint assessment	41 months	76 Gy	NA	CTCAE ver. 3.0	GI 5% GU 9%	Whole-pelvic IMRT related to GU toxicity, age to GI GI 0% if V70 ≤ 10%, V65 ≤ 20%, and V40 ≤ 40%

MSK = Memorial Sloan-Kettering Cancer Center, UPEN = University of Pennsylvania, EORTC = European Organization for Research and Treatment of Cancer, RCT = radomized controlled trial, NA = not available, CTC = Common Toxicity Criteria, CTCAE = Common Terminology Criteria for Adverse Events, RTOG = Radiation Therapy Oncology Group, GI gastrointestinal, GU; genitourinary, ED = erectile dysfunction, HR = hazard risk, SEER = Surveillance, Epidemiology and End Results, LENT/SOMA = Late Effect Normal Tissues/ Subjective, Objective, Management, and Analytic, (L/I/H) = (low risk/intermediate risk/high risk groups), *5 years unless otherwise stated.

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 ($P = 0.00093$, 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	
IMRT vs IG-IMRT								
Zelefsky [26] (MSK)	2012 ($n=376$)	IMRT vs IG-IMRT CBCT, Fiducial $n = 190$ vs 186	2.8 years	86.4 Gy	High-risk group ($n = 67$ vs 35) 3 years 77.7% 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
IGRT								
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
IG-IMRT								
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, $n = 11$ vs 48 vs 28 vs 136 vs 75 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% and V40 < 50%. They concluded that doses >78 Gy delivered using daily image guidance and IMRT are well tolerated and that by 3 months, short-term side-effects are normalized in the majority of patients.

Thus far, IGRT stays only at the preliminary stage and does not lead to reduced toxicity. Concrete evidence may come from further research.

Prognostic factors for the adverse reactions
Gastrointestinal toxicity

(i) Rectal bleeding Regardless of the type of radiation therapy, the most frequently considered functional endpoints in the published analyses are gastrointestinal (GI) toxicity complications and rectal bleeding (Table 4) [32–66]. Reported risk factors for late rectal bleeding after radiotherapy include hypertension [32], advanced age [32, 33], larger irradiated rectal volume [34, 35], a history of a prior abdominal surgical procedure [36–40], acute toxicity (including proctitis and mucous discharge) [17, 37–39, 43, 46–53), cardiac history [40], the use of ADT [41–45], hemorrhoids [54, 55], diabetes mellitus [56–59], inflammatory bowel disease (IBD) [60]. Acute toxicity is recognized as an independent significant factor confirmed in several trials. The question arises as to whether early interventions that lessen acute toxicity may also reduce the risk of late complications, or whether greater than expected acute toxicity may be an early indicator of a patient's hypersensitivity to radiotherapy.

Significant differences exist among studies in terms of techniques, procedures, definitions of the rectum (including filling, surface and wall), and the potential impact of set-up motion. Nevertheless, there are several well-established significant volume effects for partial irradiation to the rectum. The volume of the rectum receiving ≥60 Gy is consistently associated with a risk of Grade ≥2 rectal toxicity or rectal bleeding [36, 40, 45, 46, 50, 51, 56, 59–65). Several studies support a correlation between Grade 2–3 bleeding and both high (volume receiving >70 Gy [V70]) and intermediate (V50–V60) doses if a higher dose (>78 Gy) was prescribed [2, 36, 46, 51, 55, 59–65]. The conservative dose–volume constraints are V50 < 45–55%, V60 < 35–45%, V65 < 25%, V70 < 15–25% and V75 < 5–15%, although these constraints have yet to be validated as relatively safe [15, 22, 36, 40, 50–53, 59–65]. For typical dose–volume histograms (DVHs), the normal tissue complication probability (NTCP) models predict that following these constraints should limit Grade ≥2 late rectal toxicity to < 15% and the probability of Grade ≥3

late rectal toxicity to < 10% for prescriptions of up to 79.2 Gy in standard 1.8–2-Gy fractions. The parameters for the Lyman–Kutcher–Burman normal tissue complication probability model were estimated {$n = 0.09$ (95% CI: 0.04–0.14); $m = 0.13$ (0.10–0.17); and $TD_{50} = 76.9$ (73.7–80.1) Gy}. Clinicians should strive to minimize the V70 and V75 volumes below the recommended constraints without compromising tumor coverage. 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:

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% ⇒ 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 symptoms [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 ≤ 50%, V70 ≤ 35%, V75 ≤ 25%, V80 ≤ 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% < 50 Gy, D60–70 <70 Gy, D90 < 50 Gy ⇒ 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.

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 anorectal region. For example, the anal canal was contoured by taking the caudal 3 cm of the anorectal portion [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

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]. Gulliforde 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

60 134 patients who received radiation therapy with 25 904 who underwent observation.

High-dose irradiation and/or hormonal therapy result in excellent outcomes, not only in PSA control, but also in overall survival. Nguyen *et al.* reported good 5- and 10-year actuarial overall survival rates (no ADT plus 75.6 Gy, 87.3% and 72.0% respectively; and ADT plus 75.6 Gy, 92.3% and 72% respectively; $P = 0.0035$) [4]. We also obtained similar results: 70 Gy plus ADT achieve 91–93% of overall survival after 5 years [7, 93]. Therefore, we should pay attention to adverse effects and quality of life (QOL) rather than disease control because almost 90% of the patients after EBRT live longer than 5 (or 10) years.

Multiple health-related QOL studies have been conducted using the IPSS, IIEF, and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Prostate Cancer 25 items (QLQ-PR25) etc. Such comparison between radical prostatectomy, EBRT, BT, and combined approaches uncovers a link between observed toxicity and QOL. For example, Sanda *et al.* prospectively measured outcomes reported by 1201 patients and 625 spouses or partners at multiple centers before and after radical prostatectomy, BT or EBRT [94]. Adjuvant ADT is associated with worse outcomes across multiple QOL domains among patients receiving BT or radiotherapy. Patients in the BT group report long-lasting urinary irritation, bowel and sexual symptoms, and transient problems with vitality or hormonal function. Adverse effects of prostatectomy on sexual function are mitigated by nerve-sparing procedures. After prostatectomy, urinary incontinence is frequent, but urinary irritation and obstruction are improved, particularly in patients with a large prostate. No treatment-related deaths occurred in that study; serious adverse events were rare. Their results suggest that treatment-related symptoms are exacerbated by obesity, large prostate size, high PSA score and older age. Black patients report a lower degree of satisfaction with the overall treatment outcomes. Changes in QOL are significantly associated with the degree of outcome satisfaction among patients and their spouses or partners. However, there are several problems with the use of QOL questionnaires. For example, the IPSS is considered a major QOL questionnaire in the treatment of prostate cancer, but IPSS was constructed mainly for prostate hypertrophy symptoms. Thus, this questionnaire cannot evaluate adverse effects after prostatectomy (the IPSS of most patients improves after prostatectomy). Therefore, when it comes to comparison of different treatment methods, accurate QOL evaluation is a challenge.

The impact of age on prostate cancer outcomes was found not only in PSA control and survival but also in QOL in less aggressive prostate cancers in older men [95], independent of other clinical features. When adjusted for other covariates, age >70 years still correlates with decreased OS (HR, 1.56 [95% CI] 1.43–1.70 $P < 0.0001$) and with a decreased

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.

ACKNOWLEDGEMENTS

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