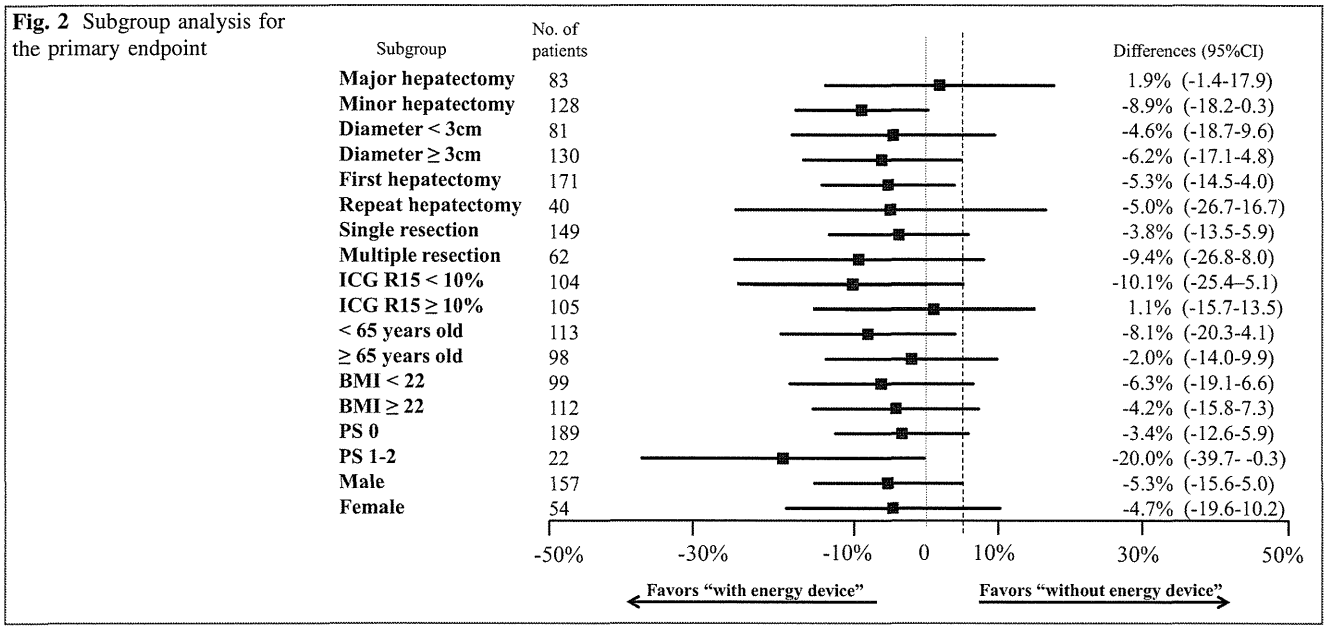


**Fig. 2** Subgroup analysis for the primary endpoint

especially intraoperative blood loss and morbidity. Since most of the ligation could be omitted during liver parenchymal transection using the energy device, we seemed to be able to perform liver resections quickly. Using energy devices during hepatectomy would be worth the cost if non-inferiority of primary endpoint and superiority of factors of the secondary endpoints were verified. Thus, we tried to verify it by the non-inferiority test. The results indicate that group E is non-inferior to group C in terms of blood loss. Although the superiority of group E could not be established, we found a shorter liver transection time and a smaller number of ties in group E as compared to group C. Our results are in accordance with those of previous studies [5, 9]. The intraoperative use of energy devices had no influence on postoperative laboratory data, suggesting no substantial heat damage in group E.

The proportion of patients with the intraoperative blood loss >1,000 mL was defined as primary endpoint, not the pure estimated blood loss. The median amounts of intraoperative blood loss were mostly less than 1,000 mL in previous studies of comparative liver transection techniques [4]. The proportion of patients with the intraoperative blood loss >1,000 mL seemed to have more clinical impact as compared to the pure estimated blood loss. That is why the blood loss >1,000 mL raises a concern about blood transfusion.

Regarding postoperative outcomes, we found significantly lower incidence of postoperative bile leakage in group E as compared to group C. Although tiny bile ducts are difficult to ligate in the complicated liver transection plane, previous studies found that energy devices were efficient to achieve bilistasis [6, 14–16]. The ability of energy devices to seal exposed tiny vessels would be advantageous for surgeons during liver parenchymal transection. UAD and vessel sealing device (VSD) are not equivalent from points of view of mechanism and feeling of handling although both energy devices have the ability to seal. There is no trial that compared outcomes of hepatectomy between UAD and VSD. There are some reports that surgical outcomes of hepatectomy with either device were superior to hepatectomy without any devices [5, 7, 8, 17]. The energy device used during hepatectomy was different with each participating institution before this study has started although choice of an energy device was fixed in each institution. Using an easy-to-use device of each liver surgeon seemed to be important to obtain outcomes close to clinical practice. Then, we approved two different devices during liver transection when we conducted this study in the multicenter.

Previous studies have also reported lower incidence of postoperative bile leakage in surgical operations with energy devices than without energy devices; however, the results did not reach statistical significance possibly due to insufficient sample sizes [5, 7, 9].

Subgroup analysis revealed a decreasing trend of blood loss in the energy device group for all subsets other than major hepatectomy (resection of ≥2 segments) and ICG R15 ≥10 %. Most major bleedings can be caused from injuries of hepatic veins in the parenchymal transection plane. In major hepatectomy, such as hemihepatectomy, major hepatic veins are often exposed in the parenchymal transection plane. Major hepatectomy was identified to be risk factor associated with blood loss >1,000 mL by multivariate analysis in Table 4. In fact, Riediger et al. [18] reported a statistically significant difference in need for intraoperative transfusion between major (≥3 segments resected) and minor hepatic resections. Even with an

energy device during hepatectomy, the amount of blood loss may increase rapidly with injuries of major hepatic veins in the parenchymal transection plane. Furthermore, it is not easy to achieve hemostasis in the parenchymal transection of patients with liver cirrhosis as this condition can be prone to bleeding.

In conclusion, we have demonstrated that the use of energy devices, such as UAD or bipolar vessel sealing device, during liver parenchymal transection is clinically meaningful. Moreover, not only in open surgeries as in the current trial, but our results also support the use of energy devices in laparoscopic surgeries, which are rapidly gaining wider acceptance in the field of liver surgery [19–21].

**Acknowledgments** The authors express deep gratitude to Dr. Tomoo Kosuge for his help and encouragement. We thank Drs. Junichi Arita, Takashi Mizuno, and Shutaro Hori for their various supports. Finally, we thank all patients and their families who participated in this study.

**Disclosure** This study was supported by a grant-in-aid for Cancer Research from the Ministry of Health, Welfare, and Labor of Japan (21-7-5).

**Conflicts of interest** The authors declare that they have no conflicts of interest to disclose.

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Cancer Science
Japanese Cancer Association JCA
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# Phase II study of zoledronic acid combined with docetaxel for non-small-cell lung cancer: West Japan Oncology Group

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**Key words**

Chemotherapy, docetaxel, non-small-cell lung cancer, phase II, zoledronic acid

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**Funding information**

Haruyasu Murakami received research funding from Sanofi K.K. and Novartis Pharma K.K. Takashi Seto received research funding from Novartis Pharma K.K. Yoichi Nakanishi received research funding from Novartis Pharma K.K. and others from Novartis Pharma K.K.

Received January 2, 2014; Revised May 12, 2014; Accepted May 14, 2014

*Cancer Sci* **105** (2014) 989–995

doi: 10.1111/cas.12448

**The aim of this open-label, multicenter, randomized phase II trial was to evaluate the efficacy and safety of zoledronic acid in combination with docetaxel in previously treated patients with non-small-cell lung cancer (NSCLC) and bone metastases. In this study, patients randomly received docetaxel (60 mg/m$^2$) with (group DZ) or without (group D) zoledronic acid every 21 days. There were 50 patients in each group, and the primary endpoint was progression-free survival. In an efficacy analysis of 94 patients (DZ, 48; D, 46), the median progression-free survival was 2.7 months (95% confidence interval [CI], 1.5–3.5 months) for the DZ group and 2.6 months (95% CI, 1.5–3.4 months) for the D group (stratified log-rank test, $P = 0.89$). The median overall survival was 10.4 months (95% CI, 7.0–15.8 months) for the DZ group and 9.7 months (95% CI, 6.1–12.5 months) for the D group (stratified log-rank test, $P = 0.62$). There were no clinically relevant differences in the frequencies of grade 3 or 4 adverse events between the two groups. No treatment-related deaths occurred in the DZ group. Zoledronic acid combined with docetaxel was well tolerated but did not meet the primary endpoint of demonstrating a longer progression-free survival in advanced NSCLC patients with bone metastases compared with docetaxel alone. This trial was registered with the University Hospital Medical Information Network (UMIN000001098).**

Lung cancer is the leading cause of cancer death worldwide and non–small-cell lung cancer (NSCLC) accounts for more than 80% of all cases of lung cancer.[1] For individuals with advanced NSCLC, first-line treatment with platinum-based chemotherapy offers only a moderate improvement in survival and quality of life over best supportive care (BSC) alone.[2,3] Second-line treatment with docetaxel, despite a low tumor response rate, is a standard treatment option on the basis of phase III studies comparing docetaxel with ifosfamide, vinorelbine or BSC alone.[4,5] Thus, there is a need for new treatment options to prolong the survival of patients with advanced NSCLC. Approximately 30–40% of patients with NSCLC develop bone metastases, which often cause skeletal-related events (SRE) such as pathologic fracture, spinal cord compression, or the need for palliative radiation or surgery to the bone.[6] SRE are associated with decreased quality of life, increased health-care costs and poor survival; therefore, it is clinically imperative to prevent SRE during the treatment of advanced NSCLC.[7–10]

Zoledronic acid, a nitrogen-containing bisphosphonate, significantly delays the appearance of SRE and reduces the incidence of SRE compared with a placebo in patients with cancer and bone metastases, including those with NSCLC.[11,12] Furthermore, several preclinical and clinical studies provide evidence supporting the use of zoledronic acid for the treatment of patients with advanced NSCLC.[13–16] The inclusion of zoledronic acid in chemotherapy regimens has an additive and/or synergistic antitumor effect on NSCLC cell lines and may prolong survival and delay disease progression in patients with advanced NSCLC.[17–19] However, whether the inclusion of zoledronic acid in such regimens has clinically meaningful survival benefits in patients with NSCLC and bone metastases is uncertain. Therefore, we

conducted this study to evaluate the efficacy and safety of zoledronic acid in combination with docetaxel in previously treated patients with NSCLC and bone metastases.

## Patients and Methods

**Study design.** We conducted an open-label, multicenter, randomized phase II study in Japan. The study protocol was approved by the West Japan Oncology Group (WJOG) Protocol Review Committee and the institutional review board of each participating institution. This trial was registered with the University Hospital Medical Information Network (UMIN000001098).

**Eligibility criteria.** Patients were required to be histologically or cytologically diagnosed with NSCLC and bone metastases (at least one bone metastasis that had not been treated with radiation therapy) and to have had previous treatment with one or two chemotherapy regimens. Other inclusion criteria included an age of ≥20 years, Eastern Cooperative Oncology Group performance status of 0–2, measurable disease, no history of chemotherapy with docetaxel, no history of prior treatment with zoledronic acid, adequate baseline organ function (leukocyte count ≥3500/mm$^3$; absolute neutrophil count ≥2000 /mm$^3$; hemoglobin ≥9.0 g/dL; platelet count ≥100 000/mm$^3$; total bilirubin ≤2.0 mg/dL; aspartate aminotransferase and alanine aminotransferase [ALT] levels ≤100 IU/L; creatinine clearance, ≥30 mL/min; and $SpO_2$ under room air, ≥90%). Written informed consent was obtained from all patients. Patients were ineligible if they had active concomitant malignancy, third-space fluid collection requiring drainage, radiographic signs of interstitial pneumonia or pulmonary fibrosis, active SRE at the time of registration, hypercalcemia requiring prompt treatment, active periodontal disease or severe comorbidities (active infectious disease, severe heart disease, uncontrolled diabetes mellitus, gastrointestinal bleeding, intestinal paralysis, bowel obstruction or psychiatric disease), or a history of drug allergy. Patients receiving systemic steroid medication and pregnant or breast-feeding women were also excluded.

**Treatment.** Equal numbers of patients randomly received 60 mg/m$^2$ docetaxel intravenously for 1 h with (DZ group) or without (D group) intravenous zoledronic acid for 15 min. Random assignment was stratified by institution, gender and performance status (0–1 or 2). The dose of zoledronic acid for each patient was based on his or her creatinine clearance (>60 mL/min, 4 mg; 50–60 mL/min, 3.5 mg; 40–49 mL/min, 3.3 mg; 30–39 mL/min, 3.0 mg). Zoledronic acid was administered to patients in the DZ group immediately after docetaxel administration. Patients were treated every 3 weeks until their disease progressed, toxicity became intolerable or they refused additional treatment. The dose of docetaxel was decreased to 50 mg/m$^2$ if any of the following was observed: leukocyte count <1000/mm$^3$, platelet count <25 000/mm$^3$, grade 3 febrile neutropenia or grade 3 nonhematological toxicity (with the exception of hyponatremia, hypocalcaemia and alopecia). In cases of grade 4 nonhematological toxicity or continued toxicity requiring a second dose reduction, the protocol treatment was terminated. Other criteria for protocol treatment termination included use of excluded concomitant therapy and physician recommendation.

Patients received full supportive care as required, including transfusion of blood products. Granulocyte colony-stimulating factor was administered as needed. There was no restriction on subsequent chemotherapy after disease progression in this study.

**Evaluation.** Patient assessment, including physical examination, complete blood count and biochemistry, was performed every 1–2 weeks. Bone markers and levels of urinary N-terminal telopeptide of type I collagen (NTX) and serum C-terminal telopeptide of type I collagen (I-CTP) were evaluated every 4 weeks. SRE included pathologic fracture, spinal cord compression and need for palliative radiation or surgery to the bone, and were assessed every 6 weeks.

Patients who received one or more protocol treatment were evaluated for safety during treatment. Adverse events were recorded and graded using the Common Terminology Criteria for Adverse Events, Version 3.0. The Response Evaluation Criteria in Solid Tumors guideline version 1.0 was used to evaluate tumor response.[20] Computed tomography was performed at baseline and every 6 weeks. A complete response (CR) or a partial response (PR) was confirmed at least

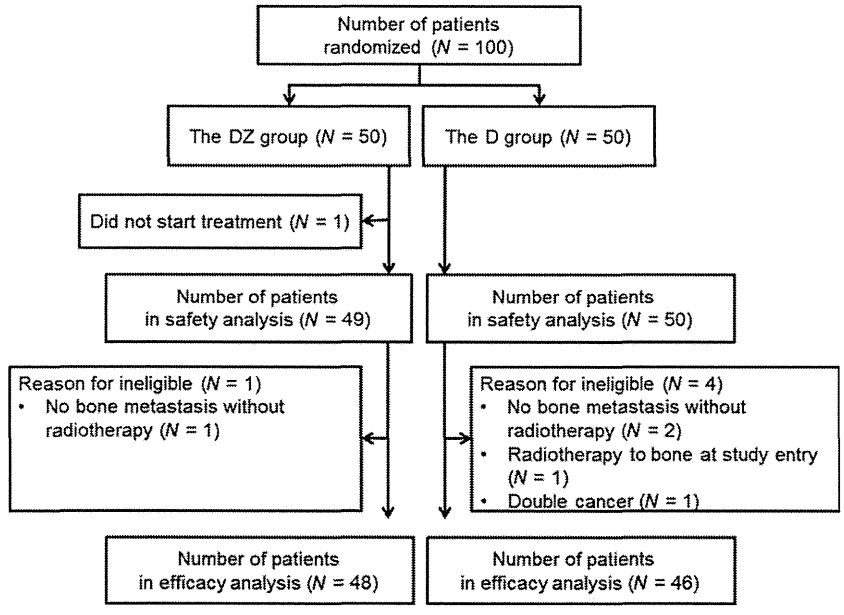


**Fig. 1.** Patient disposition. D, docetaxel alone; DZ, docetaxel with zoledronic acid.

4 weeks after the first documentation of the response. Stable disease (SD) was defined as either sufficient tumor shrinkage to qualify as a CR or a PR or sufficient increase in tumor mass to qualify as progressive disease (PD) after at least 6 weeks. Progression-free survival (PFS) was defined as the time from patient registration to objective tumor progression or patient death. Patients whose disease had not progressed at the time of termination of protocol treatment were assessed until progression or death was documented. SRE-free survival was defined as the time from patient registration to the appearance of SRE or the death of the patient. Patients who had not experienced SRE at the time of termination of protocol treatment were assessed until SRE or death was documented. Overall survival (OS) was defined as the time from patient registration to death from any cause. All patients were followed up for 1 year after the last patient had enrolled.

**Study endpoints and statistical analyses.** The primary endpoint in this study was PFS. The secondary endpoints included OS, overall response rate (ORR), SRE rate, SRE-free survival and safety. This randomized phase II study was designed to detect a 1-month improvement in PFS, with an assumed PFS of 2 months in the D group and 3 months in the DZ group, with a two-sided alpha error of 20% and a power of approximately 80%. A total of 100 patients were registered over 2 years with a 1-year follow-up period after the last enrollment. Survival curves were estimated using the Kaplan–Meier method and compared by log-rank test. Fisher's exact test was used for categorical data. All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

## Results

**Patient characteristics.** From May 2007 to March 2010, 100 patients from 15 Japanese institutions were enrolled in this study: 50 patients were randomly assigned to the DZ group and 50 to the D group (Fig. 1). Patient demographics and baseline disease characteristics were well-balanced between the two treatment groups (Table 1). While one patient in the DZ group did not receive any protocol treatment, 99 patients (49 for DZ and 50 for D) were assessable for safety. In the DZ group 1 patient and in the D group 4 patients were ineligible, and 94 patients (48 for DZ and 46 for D) were included in the efficacy analysis (Fig. 1). The median number of treatment cycles was three for the DZ group (range, 1–19 cycles) and three for the D group (range, 1–17 cycles). The median number of administered doses of zoledronic acid was 3 (range, 1–19), with a median drug exposure of 12.0 mg (range, 3.5–76.0 mg). Reasons for going off protocol included disease progression (37 for DZ and 33 for D), patient refusal (eight for DZ and eight for D), unacceptable toxicity (two for DZ and five for D) and others (two for DZ and four for D).

**Safety.** Adverse events for the 99 patients included in the safety analysis are summarized in Table 2. The occurrence of adverse events was similar in the two groups, with the exception of any grade of hypocalcemia (76% *vs* 30%) and pyrexia (39% *vs* 10%), which were more frequent in the DZ group compared with the D group. One patient in the DZ group experienced periodontal disease, but no cases of osteonecrosis of the jaw (ONJ) were observed in either group. The most common adverse events worse than grade 3 were leukopenia (63% and 56% for DZ and D, respectively), neutropenia (78% and 80% for DZ and D, respectively), febrile neutropenia (4% and 12% for DZ and D, respectively) and elevated ALT level (27% and 30% for DZ and D, respectively). There were no clinically relevant differences in the frequencies of adverse events of grade 3 or higher between the two groups. The protocol treatment was terminated in seven patients because of unacceptable toxicity levels, including grade 3 nail change ($N = 1$) and grade 2 periodontal disease ($N = 1$) in the DZ group, and required a second dose reduction because of grade 4 leukopenia ($N = 1$) or grade 3 febrile neutropenia ($N = 1$), grade 4 infection ($N = 1$), grade 3 allergic reaction ($N = 1$) and grade 1 pneumonitis ($N = 1$) in the D group. No treatment-related deaths were observed in the DZ group, while two treatment-related deaths were observed in the D group (infection, $N = 1$; gastrointestinal perforation, $N = 1$).

**Efficacy.** For the 94 patients included in the efficacy analysis, the ORR was 8% for the DZ group (CR, $N = 0$; PR, $N = 4$;

**Table 1. Patient demographics and baseline disease characteristics**

| Characteristic | DZ group ($N = 50$) | | D group ($N = 50$) | |
|---|---|---|---|---|
| | Number | % | Number | % |
| Age, years | | | | |
| Median | 62 | | 63 | |
| Range | 34–77 | | 45–79 | |
| Sex | | | | |
| Female | 19 | 38 | 18 | 36 |
| Male | 31 | 62 | 32 | 64 |
| ECOG performance status | | | | |
| 0–1 | 47 | 94 | 47 | 94 |
| 2 | 3 | 6 | 3 | 6 |
| Smoking status | | | | |
| Smoker | 19 | 38 | 15 | 30 |
| Never smoked | 31 | 62 | 35 | 70 |
| Histological subtype | | | | |
| Adenocarcinoma | 39 | 78 | 38 | 76 |
| Squamous cell carcinoma | 5 | 10 | 7 | 14 |
| Others | 6 | 12 | 5 | 10 |
| Number of prior chemotherapies | | | | |
| 1 | 34 | 68 | 39 | 78 |
| 2 | 15 | 30 | 11 | 22 |
| No data | 1 | 2 | 0 | 0 |
| Number of bone metastases | | | | |
| Single | 11 | 22 | 12 | 24 |
| Multiple | 39 | 78 | 38 | 76 |
| Prior SRE | | | | |
| No | 41 | 82 | 42 | 84 |
| Yes | 8 | 16 | 8 | 16 |
| No data | 1 | 2 | 0 | 0 |
| Urinary NTX | | | | |
| High level (≥64 nmol/mmol creatinine) | 20 | 40 | 22 | 44 |
| Normal level (<64 nmol/mmol creatinine) | 23 | 46 | 22 | 44 |
| No data | 7 | 14 | 6 | 12 |
| Serum I-CTP | | | | |
| High level (≥4.5 ng/mL) | 35 | 70 | 35 | 70 |
| Normal level (<4.5 ng/mL) | 8 | 16 | 9 | 18 |
| No data | 7 | 14 | 6 | 12 |

D, docetaxel alone; DZ, docetaxel with zoledronic acid; ECOG, Eastern Cooperative Oncology Group; I-CTP, C-terminal telopeptide of type I collagen; NTX, N-terminal telopeptide of type I collagen; SRE, skeletal-related event.

**Table 2. Summary of adverse events (CTCAE)**

| Adverse event | DZ group ($N$ = 49) | | | | D group ($N$ = 50) | | | |
|---|---|---|---|---|---|---|---|---|
| | All | | ≥Grade 3 | | All | | ≥Grade 3 | |
| | Number | % | Number | % | Number | % | Number | % |
| Leukopenia | 45 | 92 | 31 | 63 | 47 | 94 | 28 | 56 |
| Neutropenia | 45 | 92 | 38 | 78 | 46 | 92 | 40 | 80 |
| Anemia | 33 | 67 | 3 | 6 | 31 | 62 | 3 | 6 |
| Thrombocytopenia | 2 | 4 | 0 | 0 | 5 | 10 | 0 | 0 |
| Elevated ALT level | 24 | 49 | 13 | 27 | 21 | 42 | 15 | 30 |
| Elevated AST level | 19 | 39 | 4 | 8 | 16 | 32 | 3 | 6 |
| Elevated creatinine level | 7 | 14 | 1 | 2 | 13 | 26 | 2 | 4 |
| Hypercalcemia | 2 | 4 | 0 | 0 | 8 | 16 | 1 | 2 |
| Hypocalcemia | 37 | 76 | 3 | 6 | 15 | 30 | 0 | 0 |
| Febrile neutropenia | 2 | 4 | 2 | 4 | 6 | 12 | 6 | 12 |
| Infection | 13 | 27 | 5 | 10 | 5 | 10 | 3 | 6 |
| Sensory neuropathy | 12 | 24 | 2 | 4 | 11 | 22 | 1 | 2 |
| Fatigue | 33 | 67 | 2 | 4 | 33 | 66 | 2 | 4 |
| Anorexia | 30 | 61 | 2 | 4 | 30 | 60 | 1 | 2 |
| Nausea | 20 | 41 | 1 | 2 | 23 | 46 | 0 | 0 |
| Vomiting | 8 | 16 | 1 | 2 | 8 | 16 | 0 | 0 |
| Allergic reaction | 3 | 6 | 0 | 0 | 2 | 4 | 1 | 2 |
| Gastrointestinal perforation | 0 | 0 | 0 | 0 | 1 | 2 | 1 | 2 |
| Pyrexia | 19 | 39 | 0 | 0 | 5 | 10 | 0 | 0 |
| Periodontal disease | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |

ALT, alanine transaminase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events, version 3.0; D, docetaxel alone; DZ, docetaxel with zoledronic acid.

SD, $N$ = 18; PD, $N$ = 25; not evaluable, $N$ = 1) and 4% for the D group (CR, $N$ = 0; PR, $N$ = 2; SD, $N$ = 20; PD, $N$ = 23; not evaluable, $N$ = 1). The difference in ORR between the two groups was not statistically significant ($P$ = 0.88). Median PFS was 2.7 (95% CI, 1.5–3.5) months for the DZ group and 2.6 (95% CI, 1.5–3.4) months for the D group (stratified log-rank test, $P$ = 0.89; Fig. 2a). Median OS was 10.4 (95% CI, 7.0–15.8) months for the DZ group and 9.7 (95% CI, 6.1–12.5) months for the D group (stratified log-rank test, $P$ = 0.62; Fig. 2b). No remarkable difference in PFS (Fig. 3a) or OS (Fig. 3b) was observed according to demographic characteristics (number of bone metastases, prior SRE, baseline urinary NTX and baseline serum I-CTP).

For the 94 patients included in the efficacy analysis, the cumulative incidence rates of an SRE at 3, 6, 9 and 12 months were 17%, 20%, 27% and 30%, respectively, for the DZ group, and 16%, 27%, 39% and 39%, respectively, for the D group (Fig. 4a). Median SRE-free survival was 7.2 (95% CI, 4.9–10.7) months for the DZ group and 6.0 (95% CI, 4.4–8.5) months for the D group (stratified log-rank test, $P$ = 0.84). In subset analyses of the SRE rate according to baseline bone marker levels (Fig. 4b), the cumulative incidence rates of SRE at 12 months were 44% for the DZ group ($N$ = 19) and 48% for the D group ($N$ = 19) in patients with high baseline urinary NTX levels, 24% for the DZ group ($N$ = 29) and 30% for the D group ($N$ = 27) in patients with normal or unknown baseline urinary NTX levels, 43% for the DZ group ($N$ = 34) and 38% for the D group ($N$ = 32) in patients with high baseline serum I-CTP levels, and 7% for the DZ group ($N$ = 14) and 37% for the D group ($N$ = 14) in patients with normal or unknown baseline serum I-CTP levels.

## Discussion

This is the first prospective, randomized, phase II study to evaluate the efficacy and safety of zoledronic acid in combination with docetaxel in previously treated advanced NSCLC

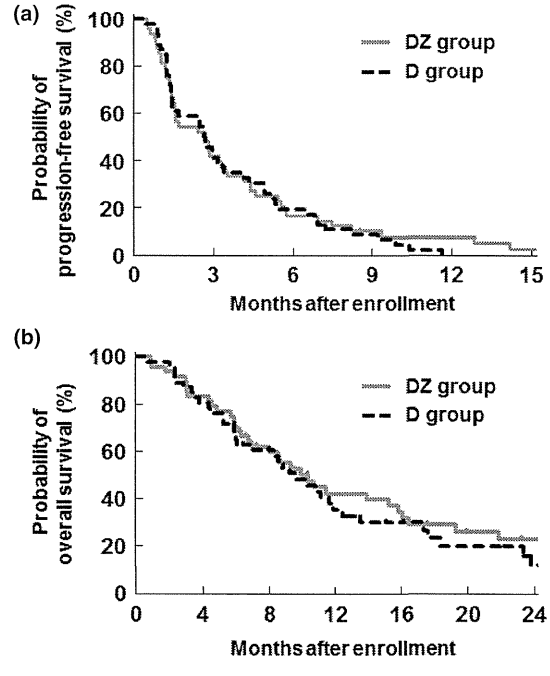


**Fig. 2.** (a) Progression-free survival and (b) overall survival in the DZ and D groups. D, docetaxel alone; DZ, docetaxel with zoledronic acid.

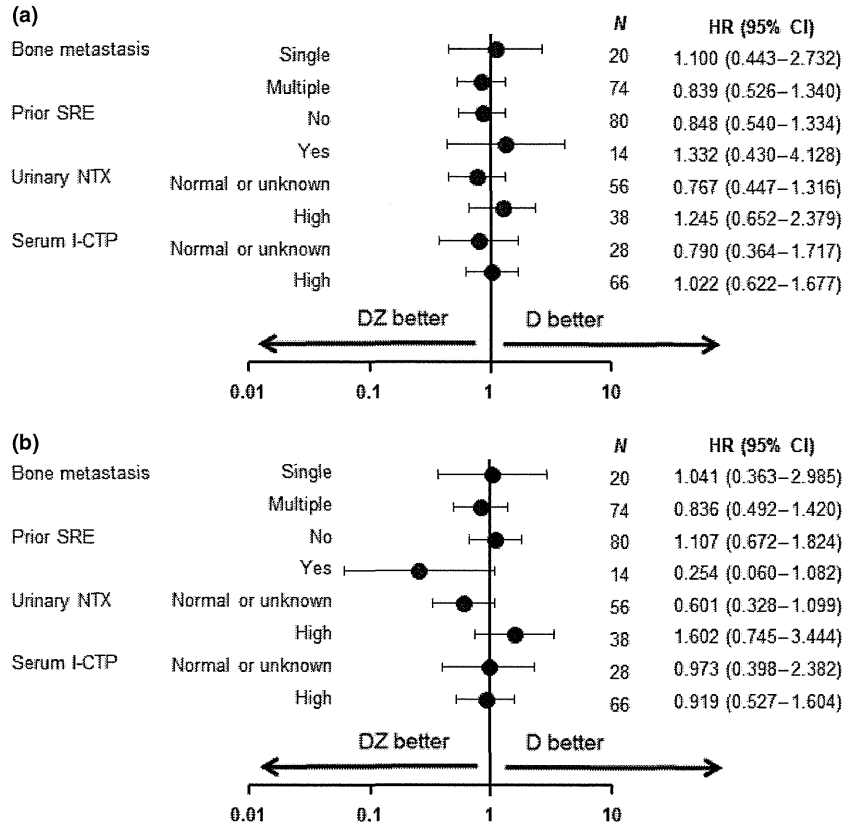


**Fig. 3.** (a) Subgroup analyses of hazard ratio for progression-free survival and (b) overall survival in the DZ and D groups. D, docetaxel alone; DZ, docetaxel with zoledronic acid; I-CTP, C-terminal telopeptide of type I collagen; NTX, N-terminal telopeptide of type I collagen; SRE, skeletal-related event.

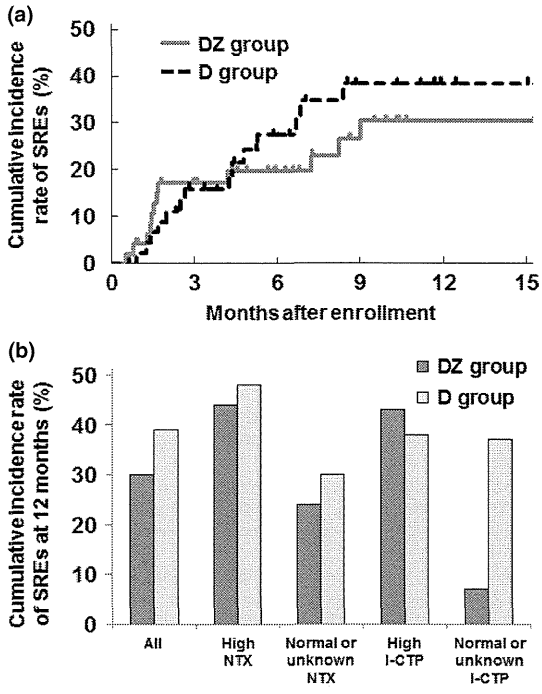


**Fig. 4.** (a) Cumulative incidence rate of SRE in the DZ and D groups. (b) Subgroup analyses of SRE rate according to baseline bone marker levels in the DZ and D groups. D, docetaxel alone; DZ, docetaxel with zoledronic acid; I-CTP, C-terminal telopeptide of type I collagen; NTX, N-terminal telopeptide of type I collagen; SRE, skeletal-related event.

patients with bone metastases. The similarity in the median PFS and OS of patients in the DZ and D groups suggests that the combination of zoledronic acid and docetaxel might not provide survival benefits to patients with NSCLC and bone metastases compared with docetaxel alone. In a previous randomized phase III study, a subgroup analysis of patients with NSCLC ($N$ = 382) revealed that zoledronic acid significantly reduced the risk of a first on-study SRE compared with a placebo. However, there was no significant difference in OS between the two groups (median 187 days for zoledronic acid *vs* 157 days for placebo; $P$ = 0.539).[11,12,14] Two randomized studies in which zoledronic acid was combined with standard treatment also showed no survival benefits for patients with NSCLC who had no bone involvement.[21,22] These results are consistent with our observation that zoledronic acid failed to prolong the survival of NSCLC patients with bone metastases. In a recent subgroup analysis of a randomized phase III study, denosumab significantly improved OS, whereas zoledronic acid did not. This analysis was conducted on a group of 811 patients with lung cancer and bone metastases (median 8.9 *vs* 7.7 months for denosumab and zoledronic acid, respectively; hazard ratio for death, 0.80; 95% CI, 0.67–0.95; $P$ = 0.01) and 702 patients with NSCLC and bone metastases (median 9.5 *vs* 8.0 months for denosumab and zoledronic acid, respectively; hazard ratio for death, 0.78; 95% CI, 0.65–0.94; $P$ = 0.01).[23,24] Denosumab, a human anti-RANKL monoclonal antibody, is a potential anticancer therapy for patients with NSCLC and bone metastases and should be evaluated further in future studies.

For patients with NSCLC and bone metastases, increased SRE risk correlated with a history of SREs, multiple bone metastases, and bone turnover markers.[25–27] Significantly high levels of urinary NTX, a sensitive bone resorption marker, were also associated with increased SRE risk and poor survival prognosis.[27] In agreement, the cumulative incidence rates of SRE were high in patients with high baseline urinary NTX levels in our study. A retrospective analysis of a phase III study revealed that zoledronic acid significantly reduces the risk of death compared with a placebo in 144 patients with NSCLC and high baseline NTX levels (hazard ratio for death, 0.65; 95% CI, 0.45–0.95; $P = 0.025$).[15] In our study, for 38 patients (19 for DZ and 19 for D) with NSCLC and high baseline NTX levels, the median OS was 8.6 months for the DZ group and 11.2 months for the D group (hazard ratio for death, 1.60; 95% CI, 0.75–3.44). Therefore, combination treatment with zoledronic acid and docetaxel did not improve OS in previously treated patients with NSCLC and bone metastases in addition to high baseline NTX levels. However, the number of patients in our study was small; as such, this study was not powered to detect differences in secondary variables, and statistical testing was performed for exploratory purposes.

The most common severe toxicities in the present study were leukopenia, neutropenia, febrile neutropenia and elevated ALT levels, which were similar in the two groups. No treatment-related deaths were observed in the DZ group. Although hypocalcemia and pyrexia were more frequent in the DZ group than in the D group, they were mild and manageable in most cases. A possible reason for the high incidence of hypocalcemia in this study was underuse of calcium supplements and vitamin D. Prophylactic oral administration of daily calcium supplements and vitamin D should be considered during treatment with zoledronic acid. No patient experienced ONJ in this study, although it may be argued that the duration of zoledronic acid treatment was too short for this to occur. No additional adverse events were observed in the present study compared with previous studies.[11,12,23,24]

The present study demonstrated the safety and tolerability of the combination of zoledronic acid and docetaxel but did not meet the primary endpoint of PFS in advanced NSCLC patients with bone metastasis. Based on these results, we abandoned assessment of the survival benefits of adding zoledronic acid to docetaxel treatment in a larger phase III study. There are potential limitations to our study. First, we used an open-label study design despite the use of PFS as the primary endpoint. Second, the sample size of the present study was relatively small. Third, we did not collect data regarding post-study treatment with zoledronic acid. New treatment options are still needed to prolong the survival of advanced NSCLC patients with bone metastasis.

## Acknowledgments

The authors would like to thank Ms Kaori Mori and Mr Koichi Hosoda for data management and Dr Shinichiro Nakamura (WJOG Data Center) for oversight and management of the present study. The authors are also grateful to Dr Keisuke Tomii (Kobe City Medical Center General Hospital, Hyogo), Dr Hideo Saka (National Hospital Organization Nagoya Medical Center, Aichi), Dr Yasuo Iwamoto (Hiroshima City Hospital, Hiroshima), Dr Norihiko Ikeda (Tokyo Medical University Hospital, Tokyo), Dr Sunao Ushijima (Kumamoto Chuo Hospital, Kumamoto), Dr Masaaki Kawahara (Otemae Hospital, Osaka), Dr Takashi Kijima (Osaka University Hospital, Osaka) and Dr Shigeki Sato (Nagoya City University Hospital, Aichi) for their contributions to this study.

## Disclosure Statement

Haruyasu Murakami received research funding from Sanofi K.K. and Novartis Pharma K.K. Takashi Seto received research funding from Novartis Pharma K.K. Yoichi Nakanishi received research funding from Novartis Pharma K.K. and others from Novartis Pharma K.K.

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Journal of Radiation Research, 2014, 55, 1033–1047
doi: 10.1093/jrr/rru061 Advance Access Publication 8 September 2014

Review Article

# 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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(Received 20 February 2014; revised 27 May 2014; accepted 9 June 2014)

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% $P=0.000\,7$ | 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 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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 74 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 = radomized 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% $P \leq 0.001$ 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%<br>GU 9% | Whole-pelvic IMRT related to GU toxicity, age to GI<br>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 ($P = 0.000\,93$, 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 | |
|---|---|---|---|---|---|---|---|---|
| **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 anorectal 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