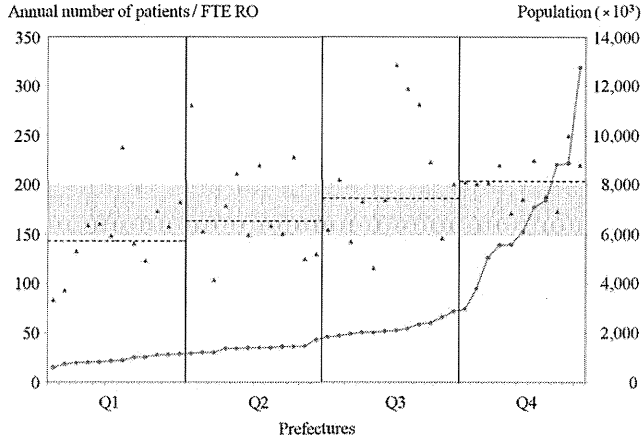

Fig. 3. Geographic distribution for 47 prefectures of annual number of patients (new plus repeat) per RO in ascending order of prefectural population. Q1: 0–25%; Q2: 26–50%; Q3: 51–75%; Q4: 76–100%. Triangles represent average annual number of patients per RO for each prefecture. Blue circles show prefectural population. Horizontal broken lines indicate the average annual number of patients per RO per quarter. The shaded area represents the Japanese Blue Book guideline (150–200 patients per RO). *Abbreviations:* RO = radiation oncologist; FTE = full-time equivalent (40 hours per week for radiation oncology services only).

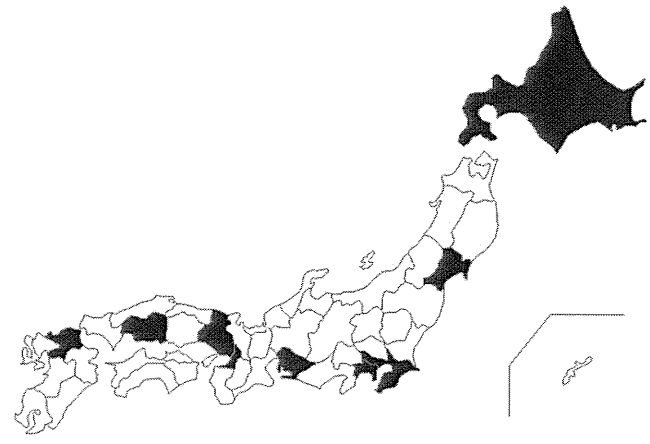

Fig. 4. The top 10 prefectures with ROs who treated more than 200 patients in descending order: Tokyo, Osaka, Kanagawa, Hokkaido, Chiba, Aichi, Fukuoka, Hyogo, Miyagi, and Hiroshima. *Abbreviation:* RO = radiation oncologist.

the same as in the United States and European countries. The shortage of ROs is not the only reason for the problems facing Japan. The pay system of ROs is another important reason. The salary of ROs in Japan is low because specialist medical fees for ROs are not covered by the Japanese healthcare insurance system. Moreover, the salary of ROs in university hospitals is lower than in other types of facilities, so that most of these ROs must work part-time at affiliated hospitals to earn a living. One advantage of this system, however, is that advanced technology is introduced sooner and faster in affiliated hospitals.

The geographic patterns demonstrated significant differences in the patient load among prefectures, ranging from 83.2 to 321.4 patients per RO. There were more ROs in metropolitan than other areas. However, the number of ROs who had more than 200 patients (new plus repeat) was strongly associated with population (correlation coefficient: 0.94), so that the number of ROs in metropolitan area remained insufficient.

Gomi *et al.* reported that the survival rate of patients treated in academic RT facilities (university hospitals and cancer centers) was better than that of those treated in nonacademic RT facilities in Japan (10). In this study, the proportion of facilities with part-time ROs in nonacademic RT facilities group was higher than that in academic RT facilities group. Part-time ROs have less care time per patient because they had a limit to working hours. On the basis of the presented evidence, the relative practice index for patients of ROs was calculated as one way to valuate quality of cancer care in this study. Concerning ROs working primarily in university hospitals, the average relative practice index for patients in affiliated facilities was less than that in main facilities (university hospitals). Teshima *et al.* reported that academic RT facilities (university hospitals and cancer centers) had better equipments and manpower than nonacademic RT facilities (1). Therefore, ROs at large-scale university hospitals might be given sufficient support because large-scale university hospitals tend to have state-of-the-art equipment, practice leading-edge medical treatment techniques, and employ enough medical staff members. On the other hand, ROs of most affiliated facilities could provide only minimal cancer care because these facilities

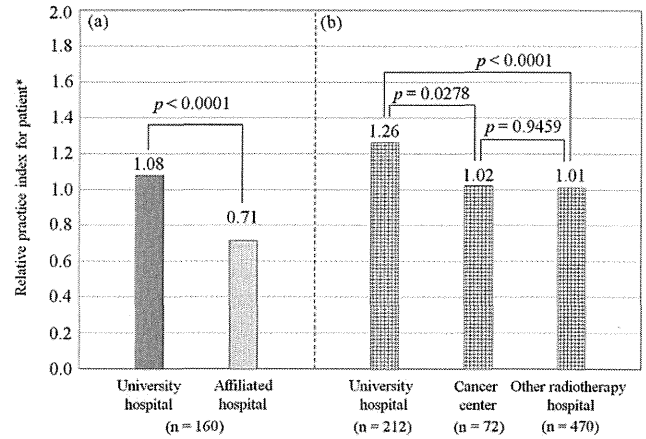

Fig. 5. Relative practice index for patients of ROs. (a) Relative practice index for patients in university hospitals and affiliated hospitals (targeted ROs were working mainly in university hospitals and part-time in affiliated hospitals). (b) Relative practice index for patients in university hospitals, cancer centers, and other radiotherapy hospitals (targeted ROs were working only in university hospitals or cancer centers only or only in other radiotherapy hospitals). *The formula used for calculating relative practice index for patients is: $\frac{\sum_{k=1}^{n} f_k}{\sum_{k=1}^{n} a_k} \times 200$ n: number of facilities that the RO works in (n = 1, 2, 3, ..., k). f_k : FTE of the RO in facility k a_k : annual number of patients per RO in facility k. *Abbreviations:* RO = radiation oncologist; FTE = full-time equivalent (40 hours per week for radiation oncology services only).

tend to lack sufficient equipment and medical staff. Moreover, commuting between large-scale university hospitals and affiliated facilities resulted in a waste of time and in tiredness. Therefore, the quality of cancer care in affiliated facilities was worse than that in large-scale university hospitals. Although the annual number of patients per RO in cancer centers was higher than that in university hospitals and other RT hospitals, the average relative practice index for patients of ROs working only in cancer centers was lower than that for patients of ROs working only in university hospitals and equal to that for patients of ROs working only in other RT hospitals. It can thus be concluded that ROs in cancer centers worked efficiently.

The utilization rate of RT for new cancer patients in Japan is much lower than that in European countries and the United States. Because there are enough RT facilities distributed nationwide in Japan, an increase in the number of Ros would likely result in a spectacular improvement in the utilization rate of RT for new cancer patients. To increase the number of ROs, it is necessary to improve the work environment and conditions for radiation oncology in medical care facilities. One, feasible suggestion is for RT facilities to set up a new department of radiation oncology, so that the position of RO will be established at every such facility and the status of radiation oncology will improve as a result. In addition, the Cancer Control Act was approved in 2006 and the Basic Plan to Promote Cancer Control Program was approved by the Japanese Cabinet in 2007 to promote RT and education for ROs as well as other RT staff members. For the implementation of this law and plan, the availability of basic data of RO working conditions is essential. As a start, an education program called "Cancer Professional Training Plan" was started in April 2008 with the support of the Ministry of Education, Culture, Sports, Science and Technology.

Quality of cancer care was evaluated in this study with the aid of the relative practice index for patients. However, data concerning the processes and outcomes for cancer care using RT should be used for a more accurate evaluation of cancer care. In the United States, the National Cancer Data Base has been collecting data for cancer care. The data of National Cancer Data Base are useful for quality evaluation of cancer care (11, 12). Furthermore, PCS has been performed every 4 or 5 years since 1973 for a survey of the structure, processes, and outcomes of radiation oncology facilities (13). As PCS evolved into Quality Research in Radiation Oncology, periodic assessments of radiation oncology have been conducted for evaluation of practice quality on a national basis. In Japan, the structure, processes and outcomes for cancer care using RT have been investigated by PCS every 4 years (7, 8). The Japanese PCS has evaluated the quality of cancer care with RT and provided evidence of the disparity in quality of RT among facilities (14–18). However, these data are insufficient because PCS is a two-stage cluster sampling survey. We have recently established a database system based on available radiation oncology data and the collection of cancer care data by means of this system is now in preparation.

This study based on the JASTRO structure survey has indicated that the current national medical care system may impede fostering of true specialization of radiation oncologists in Japan because it is suffering from systemic fatigue. Although private hospitals make much money by receiving fee-for-service reimbursement, public hospitals face major deficit problems. It is therefore necessary to redistribute the burden of medical costs. On the other hand, the Japanese medical care system is beneficial for patients and national finances. Japan has had a universal health insurance system since 1961. Even though the per-capita medical costs in Japan were less than half of those in the United States and the medical costs in relation to the gross domestic product in Japan were about half of those in the United States as of 2007 (19), the outcome of cancer treatment in Japan is the same or better than in the United States. It is therefore very important to collect at regular intervals detailed information about all cancer care facilities for evaluation of quality of care and medical care systems for cancer. In Japan, the JASTRO structure survey has collected structural data of radiation oncology. Furthermore, a database system for the collection of data regarding the processes and outcomes for cancer care has recently been established in Japan as well as an information infrastructure for evaluation of the quality of care in radiation oncology.

In conclusion, our survey found that ROs working in university hospitals and their affiliated facilities treated more patients than did other ROs. In terms of patient care time only, the quality of cancer care in affiliated facilities might be worse than that in university hospitals. Under the current national insurance system, working patterns of ROs in academic facilities in Japan tend to impede the fostering of true specialization of radiation oncologists.

REFERENCES

1. Teshima T, Numasaki H, Shibuya H, *et al.* Japanese structure survey of radiation oncology in 2007 based on institutional stratification of Patterns of Care Study. *Int J Radiat Oncol Biol Phys* 2010;78:1483–1493.
2. Maeda M. A review of cancer control strategy in Japan [in Japanese]. *J Natl Inst Public Health* 2008;57:304–307.
3. Teshima T, Numasaki H, Shibuya H, *et al.* Japanese structure survey of radiation oncology in 2005 based on institutional stratification of Patterns of Care Study. *Int J Radiat Oncol Biol Phys* 2008;2:144–152.
4. SAS Institute Inc. SAS User's Guide: Statistics. Cary, NC: SAS Institute Inc.; 1985.
5. Japanese PCS Working Group. Radiation oncology in multidisciplinary cancer therapy -Basic structure requirement for quality assurance of radiotherapy based on Patterns of Care Study in Japan. Ministry of Health, Labor and Welfare Cancer Research Grant Planned Research Study 14-6, 2005.
6. Japanese PCS Working Group. Radiation oncology in multidisciplinary cancer therapy -Basic structure requirement for quality assurance of radiotherapy based on Patterns of Care Study in

Japan. Ministry of Health, Labor and Welfare Cancer Research Grant Planned Research Study 18-4, 2010.
7. Tanisada K, Teshima T, Ohno Y, *et al.* Patterns of Care Study quantitative evaluation of the quality of radiotherapy in Japan. *Cancer* 2002;95:164–171.
8. Teshima T, Japanese PCS working group. Patterns of Care Study in Japan. *Jpn J Clin Oncol* 2005;35:497–506.
9. Ministry of Internal Affairs and Communications, Statistics Bureau, Director-General for Policy Planning (Statistical Standards) & Statistical Research and Training Institute. Current population estimates as of October 1, 2007. Available from: www.stat.go.jp/english/data/jinsui/2007np/index.htm (accessed August 31, 2010).
10. Gomi K, Oguchi M, Hirokawa Y, *et al.* Process and preliminary outcome of a patterns-of-care study of esophageal cancer in Japan: Patients treated with surgery and radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;56:813–822.
11. National Cancer Data Base. Available from: www.facs.org/cancer/ncdb/index.html (accessed June 30, 2010).
12. Bilimoria KY, Stewart AK, Winchester DP, *et al.* The National Cancer Data Base: A powerful initiative to improve cancer care in the United States. *Ann Surg Oncol* 2008;15:683–690.
13. Wilson JF, Owen JB. Quality research in radiation oncology: A self-improvement initiative 30 years ahead of its time? *J Am Coll Radiol* 2005;2:1001–1007.
14. Yamauchi C, Mitsumori M, Sai H, *et al.* Patterns of care study of breast-conserving therapy in Japan: Comparison of the treatment process between 1995–1997 and 1999–2001 surveys. *Jpn J Clin Oncol* 2007;38:26–30.
15. Toita T, Kodaira T, Uno T, *et al.* Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): Patterns of Care Study in Japan. *Int J Radiat Oncol Biol Phys* 2008;70:788–794.
16. Kenjo M, Uno T, Numasaki H, *et al.* Radiation therapy for esophageal cancer in Japan: Results of the Patterns of Care Study 1999–2001. *Int J Radiat Oncol Biol Phys* 2009;75:357–363.
17. Uno T, Sumi M, Numasaki H, *et al.* Changes in patterns of care for limited-stage small cell lung cancer: Results of the 99-01 Patterns of Care Study—A nationwide survey in Japan. *Int J Radiat Oncol Biol Phys* 2008;71:414–419.
18. Ogawa K, Nakamura K, Onishi H, *et al.* Japanese Patterns of Care Study Working Subgroup of Prostate cancer. External beam radiotherapy for clinically localized hormone-refractory prostate cancer: Clinical significance of nadir prostate-specific antigen value within 12 months. *Int J Radiat Oncol Biol Phys* 2009;74:759–765.
19. OECD Health Data 2010. Paris: Organisation for Economic Co-Operation and Development; 2010.

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation

Patterns of Practice in Palliative Radiotherapy for Painful Bone Metastases: A Survey in Japan

Naoki Nakamura, M.D.,* Naoto Shikama, M.D.,† Hitoshi Wada, M.D.,‡ Hideyuki Harada, M.D.,§ Miwako Nozaki, M.D.,¶ Hisayasu Nagakura, M.D.,‖ Masao Tago, M.D., Masahiko Oguchi, M.D.,†† Nobue Uchida, M.D.‡‡, and the Japanese Radiation Oncology Study Group Working Subgroup of Palliative Radiotherapy**

**Department of Radiation Oncology, St. Luke's International Hospital, Tokyo; †Department of Radiation Oncology, Saitama Medical University International Medical Center, Hidaka; ‡Department of Radiation Oncology, Miyagi Cancer Center, Natori; §Division of Radiation Oncology, Shizuoka Cancer Center, Mishima; ¶Department of Radiology, Dokkyo Medical University Koshigaya Hospital, Koshigaya; ‖Department of Radiology, KKR Sapporo Medical Center, Sapporo; **Department of Radiology, Teikyo University Mizonokuchi Hospital, Kawasaki; ††Department of Radiation Oncology, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo; and ‡‡Department of Radiation Oncology, Shimane University Hospital, Izumo, Japan*

Received Oct 26, 2011. Accepted for publication Nov 19, 2011

Summary

To determine the current patterns of practice in Japan and to investigate factors that may make clinicians reluctant to use single-fraction radiotherapy, members of the Japanese Radiation Oncology Study Group completed an Internet-based survey and described the radiotherapy dose fractionation they would recommend for four hypothetical cases describing patients with painful bone metastases. Single-fraction radiotherapy

Purpose: To determine the current patterns of practice in Japan and to investigate factors that may make clinicians reluctant to use single-fraction radiotherapy (SF-RT).

Methods and Materials: Members of the Japanese Radiation Oncology Study Group (JROSG) completed an Internet-based survey and described the radiotherapy dose fractionation they would recommend for four hypothetical cases describing patients with painful bone metastasis (BM). Case 1 described a patient with an uncomplicated painful BM in a non-weight-bearing site from non-small-cell lung cancer. Case 2 investigated whether management for a case of uncomplicated spinal BM would be different from that in Case 1. Case 3 was identical with Case 2 except for the presence of neuropathic pain. Case 4 investigated the prescription for an uncomplicated painful BM secondary to oligometastatic breast cancer. Radiation oncologists who recommended multifraction radiotherapy (MF-RT) for Case 2 were asked to explain why they considered MF-RT superior to SF-RT.

Results: A total of 52 radiation oncologists from 50 institutions (36% of JROSG institutions) responded. In all four cases, the most commonly prescribed regimen was 30 Gy in 10 fractions. SF-RT was recommended by 13% of respondents for Case 1, 6% for Case 2, 0% for Case 3, and 2% for Case 4. For Case 4, 29% of respondents prescribed a high-dose MF-RT regimen (*e.g.*, 50 Gy in 25 fractions). The following factors were most often cited as reasons for preferring MF-RT: "time until first increase in pain" (85%), "incidence of spinal cord compression" (50%), and "incidence of pathologic fractures" (29%).

Reprint requests: Naoki Nakamura, M.D., Department of Radiation Oncology, St. Luke's International Hospital, 9-1, Akashicho, Chuouku, Tokyo, 104-8560, Japan. Tel: (+81) 3-3541-5151; Fax: (+81) 3-3544-0649; E-mail: naokinak@luke.or.jp

Presented in part at the 53rd Annual Meeting of the American Society for Radiation Oncology (ASTRO) at Miami Beach, FL, October 2–6, 2011.

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–4, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.11.075

was recommended by 0%–13% of respondents. "Time until first increase in pain" was most often cited as a reason for preferring multifraction radiotherapy.

Conclusions: Japanese radiation oncologists prefer a schedule of 30 Gy in 10 fractions and are less likely to recommend SF-RT. Most Japanese radiation oncologists regard MF-RT as superior to SF-RT, based primarily on the time until first increase in pain. © 2012 Elsevier Inc.

Keywords: Radiotherapy, Bone metastasis, Japan, Single fraction, Oligometastasis

Introduction

Radiotherapy (RT) provides successful palliation of painful bone metastasis (BM), with 50% to 80% overall response rates (1).

Numerous prospective randomized controlled trials have demonstrated the equivalence of multifraction (MF) and single-fraction (SF) RT for the palliation of painful BM (2–10). Owing to patient convenience, resource advantages, and cost effectiveness, clinical practice guidelines have recommended that SF-RT should be in widespread use (11–13).

However, according to previous surveys, SF regimens have remained underused globally (14–18). In addition, regional and national differences in prescribing patterns for painful BM have been described (15, 16). To our knowledge, no previous surveys have focused on the prescribing patterns in Japan. This study investigated the current patterns of practice in Japan and factors that may make clinicians reluctant to use SF-RT.

Methods and Materials

Members of the Japanese Radiation Oncology Study Group (JROSG) completed an Internet-based survey. All JROSG members were radiation oncologists (ROs). The respondents indicated their name, their institutions, and the radiotherapy dose fractionation they would recommend for four hypothetical cases describing patients with painful BM (Table 1). Case 1 described a patient with an uncomplicated painful BM in a non-weight-bearing site from non-small-cell lung cancer. Case 2 investigated whether management for a case of uncomplicated spinal BM would be different from that in Case 1. Case 3 was identical with Case 2 except for the presence of neuropathic pain. Case 4 investigated the prescription for an uncomplicated painful BM secondary to oligometastatic breast cancer. ROs who recommended MF-RT for Case 2 were asked to explain why they considered MF-RT superior to SF-RT.

Results

A total of 52 ROs from 50 institutions (36% of JROSG institutions) responded. Of those, 32 respondents (61%) work at university hospitals or cancer centers, 15 (29%) at public hospitals, and 5 (10%) at private hospitals.

A total of 14 different dose schedules were cited, ranging from 8 Gy in one fraction to 60 Gy in 30 fractions. The recommended treatments for Cases 1 through 4 are summarized in Table 2. In all four cases, the most commonly prescribed regimen was 30 Gy in 10 fractions. None of the respondents recommended SF-RT for neuropathic pain (Case 3). For oligometastasis (Case 4), 29% of respondents prescribed a high-dose MF-RT regimen (*e.g.*, 50 Gy in 25 fractions).

Table 3 summarizes why these respondents regarded MF-RT as superior to SF-RT for Case 2. The following factors were most often cited as reasons for preferring MF-RT: "time until first increase in pain" (85%), "incidence of spinal cord compression" (50%), and "incidence of pathologic fractures" (29%).

Discussion

Our results show that SF-RT was used by the minority of Japanese ROs, a finding consistent with previous reports from other regions or nations. Japanese ROs preferred a schedule of 30 Gy in 10 fractions.

In our study, the first case described uncomplicated BM in a non-weight-bearing site, and the second case described uncomplicated spinal BM. Both cases fit the eligibility criteria for most previously completed randomized trials (2–10). Only 13% and 6% of our respondents recommended SF-RT for Case 1 and Case 2, respectively.

As many as 85% of the respondents who recommended MF-RT for Case 2 regarded MF-RT as superior to SF-RT based on the time until first increase in pain. The randomized trials do not support the superiority of MF-RT to prevent recurrence, even with

Table 1 Hypothetical cases

Case 1	A 65-year-old man was diagnosed with squamous cell lung cancer 1 year earlier and was treated by radical surgery. He now has pain in the right shoulder. Radiologic examinations detected osteolytic bone metastasis at the right scapula and multiple lung metastases. His ECOG performance status is 1.
Case 2	A 65-year-old man was diagnosed with squamous cell lung cancer 1 year earlier and was treated by radical surgery. He now has back pain. Radiologic examinations detected osteolytic bone metastasis at L1 and multiple lung metastases. There is no evidence of vertebral collapse or of spinal or thecal sac compression. His ECOG performance status is 1.
Case 3	Same setting as in Case 2, with the addition of paresthesias in a distribution consistent with the L1 dermatome, compatible with neuropathic pain.
Case 4	A 64-year-old woman was diagnosed with breast cancer 7 years earlier and was treated by radical surgery, followed by tamoxifen. She now has pain in the right shoulder. Radiologic examinations detected solitary osteolytic metastasis at the right scapula. Her ECOG performance status is 1.

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Table 2 Recommended dose schedules for cases of painful bone metastases (BM) (n = 52)

Case	Single fraction (8 Gy), n (%)	Fractionated low dose (20 Gy in 5 fractions), n (%)	30 Gy in 10 fractions, n (%)	Fractionated intermediate dose other than 30 Gy in 10 fractions, n (%)*	Fractionated high dose, n (%)†	External beam irradiation not recommended, n (%)
Case 1: Uncomplicated peripheral BM	7 (13)	5 (10)	34 (65)	5 (10)	0 (0)	1 (2)
Case 2: Uncomplicated spinal BM	3 (6)	2 (4)	40 (77)	6 (12)	0 (0)	1 (2)
Case 3: Neuropathic pain	0 (0)	3 (6)	41 (79)	8 (15)	0 (0)	0 (0)
Case 4: Ologometastasis	1 (2)	0 (0)	26 (50)	10 (19)	15 (29)	0 (0)

* Eight different dose schedules (25 Gy in five fractions, 36 Gy in 12 fractions, 37.5 Gy in 15 fractions, 39 Gy in 13 fractions, 40 Gy in 20 fractions, 40 Gy in 16 fractions, 45 Gy in 15 fractions, and 46 Gy in 23 fractions) are included.

† Three different dose schedules (50 Gy in 25 fractions, 50 Gy in 20 fractions, and 60 Gy in 30 fractions) are included.

extended follow-up (2, 3). Higher rates of reirradiation for SF patients have been reported despite equivalent response and progression rates between SF-RT and MF-RT. This is interpreted as reflecting a lower threshold for both clinicians and patients after lower doses.

Half of our respondents who recommended MF-RT for Case 2 were concerned about the high incidence of spinal cord compression subsequent to SF-RT. Three randomized trials have reported spinal cord compression rates with uncomplicated spinal metastases, but none of the trials have shown a statistically significant difference between SF-RT and MF-RT (2, 3, 7).

Another concern about SF-RT is the risk of pathologic fracture. Twenty-nine percent of our respondents who recommended MF-RT for Case 2 were concerned about the high incidence of pathologic fracture subsequent to SF-RT. Recalcification of osteolytic bone lesions seems to be dose dependent (6). However, the contribution of recalcification to prevent fracture remains unclear. In the Dutch trials, there was a significantly higher risk of pathologic fracture in the SF arm than in the multifraction arm (24 Gy in six fractions), 4% vs. 2% (p = 0.05) (2). In the randomized trials performed in Scandinavia, however, there was a significantly higher risk in the multifraction arm (30 Gy in 10 fractions) than in the SF arm, 11% vs. 4% (5). In other randomized trials, there has not been any significant difference in the rate of pathologic fracture between SF-RT and MF-RT (3, 4, 7–9, 19).

Case 3 was identical with Case 2 except for the presence of neuropathic pain. None of our respondents recommended SF-RT. Neuropathic pain due to BM has been the subject of one randomized trial comparing an SF arm with a multifraction arm (20 Gy in five fractions). Treatment in the SF arm was not shown to be as effective as that in the multifraction arm, nor was it statistically significantly worse (19). Our study suggests that Japanese ROs considered that greater doses were needed to relieve nerve impingement or to reduce the risk of spinal cord compression.

Table 3 The basis on which respondents regarded multifraction radiotherapy superior to single-fraction therapy (48 respondents who recommended multifraction radiotherapy for Case 2)

Factor	n (%)
Response rates of pain relief	7 (15)
Time until first increase in pain	41 (85)
Survival duration	1 (2)
Quality of life	12 (25)
Pathologic fracture	14 (29)
Spinal cord compression	24 (50)
Acute side effects	9 (19)
Late side effects	7 (15)

Our final case described an uncomplicated painful BM secondary to breast cancer in which oligometastasis developed after a long disease-free interval. A considerable number of our respondents recommended a high-dose MF-RT regimen (*e.g.,* 50 Gy in 25 fractions). A practice guideline for palliative radiotherapy of metastatic breast cancer from Germany also recommends a full-dose fractionated regimen (*e.g.,* 40–50 Gy in 20–25 fractions) for oligometastases (12).

Regional and national differences in prescribing patterns for painful BM have been previously described (15, 16). SF regimens have been most frequently reported by ROs in the United Kingdom and least frequently by ROs in the United States (15, 20). Our results suggest that Japanese ROs prescribe SF-RT as often as do ROs in the United States. The reasons proposed for regional and national differences have included the influence of reimbursement and participation in related randomized controlled trials (17, 18). Reimbursement depends on the number of treatments in Japan, and most Japanese ROs have never participated in related randomized controlled trials. In addition, where ROs train has a variable effect on the patterns of treatment. Those trained in the United States were as much as 80% less likely to use SF-RT than were those trained in Canada or Europe (15). We think that Japanese ROs prefer to learn from United States resources, resulting in similar patterns of practice as those in the United States. These factors may result in the underuse of SF-RT by Japanese ROs.

Our study has certain limitations. Because of the relatively low response rate (36%) and the small absolute sample size (n = 52), our results might not accurately represent the practice of ROs in Japan. Those willing to participate might have been more knowledgeable. Furthermore, recommendations for hypothetical cases might not reflect clinical management.

Conclusions

Japanese ROs prefer a schedule of 30 Gy in 10 fractions and are less likely to recommend SF-RT. Most Japanese ROs regard MF-RT as superior to SF-RT, based primarily on the time until first increase in pain.

References

1. Chow E, Harris K, Fan G, *et al.* Palliative radiotherapy trials for bone metastases: A systematic review. *J Clin Oncol* 2007;25:1423–1436.
2. Steenland E, Leer JW, van Houwelingen H, *et al.* The effect of a single fraction compared to multiple fractions on painful bone metastases: A global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999;52:101–109.
3. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: Randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. *Radiother Oncol* 1999;52:111–121.
4. Hartsell WF, Scott CB, Bruner DW, *et al.* Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst* 2005;97:798–804.
5. Kaasa S, Brenne E, Lund JA, *et al.* Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy × 1) versus multiple fractions (3 Gy × 10) in the treatment of painful bone metastases. *Radiother Oncol* 2006;79:278–284.
6. Koswig S, Budach V. [Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy): A prospective study]. *Strahlenther Onkol* 1999;175: 500–508.
7. Price P, Hoskin PJ, Easton D, *et al.* Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986;6: 247–255.
8. Nielsen OS, Bentzen SM, Sandberg E, *et al.* Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiother Oncol* 1998;47:233–240.
9. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol (R Coll Radiol)* 1989;1:59–62.
10. Kagei K, Suzuki K, Shirato H, *et al.* [A randomized trial of single and multifraction radiation therapy for bone metastasis: A preliminary report]. *Gan No Rinsho* 1990;36:2553–2558.
11. Wu JS, Wong RK, Lloyd NS, *et al.* Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases: An evidence-based practice guideline. *BMC Cancer* 2004;4:71.
12. Souchon R, Wenz F, Sedlmayer F, *et al.* DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: Bone metastases and metastatic spinal cord compression (MSCC). *Strahlenther Onkol* 2009;185:417–424.
13. Lutz S, Berk L, Chang E, *et al.* Palliative radiotherapy for bone metastases: An ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79:965–976.
14. Ben-Josef E, Shamsa F, Williams AO, *et al.* Radiotherapeutic management of osseous metastases: A survey of current patterns of care. *Int J Radiat Oncol Biol Phys* 1998;40:915–921.
15. Fairchild A, Barnes E, Ghosh S, *et al.* International patterns of practice in palliative radiotherapy for painful bone metastases: Evidence-based practice? *Int J Radiat Oncol Biol Phys* 2009;75:1501–1510.
16. Gupta T, Sarin R. Palliative radiation therapy for painful vertebral metastases: A practice survey. *Cancer* 2004;101:2892–2896.
17. Lievens Y, Van den Bogaert W, Rijnders A, *et al.* Palliative radiotherapy practice within Western European countries: Impact of the radiotherapy financing system? *Radiother Oncol* 2000;56:289–295.
18. Roos DE. Continuing reluctance to use single fractions of radiotherapy for metastatic bone pain: An Australian and New Zealand practice survey and literature review. *Radiother Oncol* 2000;56:315–322.
19. Roos DE, Turner SL, O'Brien PC, *et al.* Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiother Oncol* 2005;75:54–63.
20. Bradley NM, Husted J, Sey MS, *et al.* Review of patterns of practice and patients' preferences in the treatment of bone metastases with palliative radiotherapy. *Support Care Cancer* 2007;15:373–385.

Acta Oncologica, 2012; 51: 730–734

informa
healthcare

ORIGINAL ARTICLE

The relationship between the bladder volume and optimal treatment planning in definitive radiotherapy for localized prostate cancer

NAOKI NAKAMURA[1], NAOTO SHIKAMA[2], OSAMU TAKAHASHI[3], KENJI SEKIGUCHI[1], YUKIHIRO HAMA[4], KEIKO AKAHANE[1] & KEIICHI NAKAGAWA[5]

[1]*Department of Radiation Oncology, St. Luke's International Hospital, Tokyo, Japan,* [2]*Department of Radiation Oncology, Saitama Medical University, Hidaka, Japan,* [3]*Division of General Internal Medicine, Department of Medicine, St. Luke's International Hospital, Tokyo, Japan,* [4]*Department of Radiology, Edogawa Hospital, Tokyo, Japan, and* [5]*Department of Radiology, Tokyo University School of Medicine, Tokyo, Japan*

Abstract

Background. There is no current consensus regarding the optimal bladder volumes in definitive radiotherapy for localized prostate cancer. The aim of this study was to clarify the relationship between the bladder volume and optimal treatment planning in radiotherapy for localized prostate cancer. *Material and methods.* Two hundred and forty-three patients underwent definitive radiotherapy with helical tomotherapy for intermediate- and high-risk localized prostate cancer. The prescribed dose defined as 95% of the planning target volume (PTV) receiving ≧100% of the prescription dose was 76 Gy in 38 fractions. The clinical target volume (CTV) was defined as the prostate with a 5-mm margin and 2 cm of the proximal seminal vesicle. The PTV was defined as the CTV with a 5-mm margin. Treatment plans were optimized to satisfy the dose constraints defined by in-house protocols for PTV and organs at risk (rectum wall, bladder wall, sigmoid colon and small intestine). If all dose constraints were satisfied, the plan was defined as an optimal plan (OP). *Results.* An OP was achieved with 203 patients (84%). Mean bladder volume (± 1 SD) was 266 ml (± 130 ml) among those with an OP and 214 ml (±130 ml) among those without an OP ($p = 0.02$). Logistic regression analysis also showed that bladder volumes below 150 ml decreased the possibility of achieving an OP. However, the percentage of patients with an OP showed a plateau effect at bladder volumes above 150 ml. *Conclusions.* Bladder volume is a significant factor affecting OP rates. However, our results suggest that bladder volumes exceeding 150 ml may not help meet planning dose constraints.

The bladder is filled to various volumes during fractionated radiotherapy. Changing bladder volumes affects both bladder dose volumes and the position of adjacent organs (the prostate, seminal vesicles, small intestine and sigmoid colon) [1]. Furthermore, significant variations in bladder volume can affect planned three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) dose distributions. For all these reasons, bladder volumes must be kept consistent throughout planning and treatment to reduce positional uncertainties related to the prostate and the risk of increased toxicity to the surrounding normal tissue.

There is no current consensus regarding the optimal bladder volumes in definitive radiotherapy for localized prostate cancer. One possible advantage of maintaining a full bladder is that part of the bladder moves away from the target volume, thereby reducing bladder toxicity [2,3]. A full bladder also moves the small intestine and the sigmoid colon out of the irradiation field, reducing toxicity in these organs [1,4–7]. However, if we target larger bladder volumes on planning using computed tomography (CT) and during radiotherapy, such volumes tend to show marked variability [8–10]. On the other hand, excessively small bladder volumes make it difficult to meet planning dose constraints for the bladder and adjacent organs. For these reasons, the optimal bladder volume may be the minimum bladder volume that can satisfy dose constraints. Based on this reasoning, several institutions target a half-full bladder or a comfortably full bladder [8,9]. However, no previous

Correspondence: N. Nakamura, Department of Radiation Oncology, St. Luke's International Hospital, 9-1, Akashicho, Chuoh-ku, Tokyo 104-8560, Japan. Tel: +81 3 35415151. Fax: +81 3 35440649. E-mail: nnakamur-tky@umin.ac.jp

(Received 30 June 2011; accepted 4 November 2011)

ISSN 0284-186X print/ISSN 1651-226X online © 2012 Informa Healthcare
DOI: 10.3109/0284186X.2011.639388

reports have focused on the relationship between the bladder volume and optimal treatment planning.

We evaluated the relationship between the bladder volume on planning CT and the percentage satisfying the dose constraints as a reference what bladder volumes should be targeted.

Material and methods

Between June 2007 and February 2009, 243 patients underwent definitive radiotherapy with helical tomotherapy using the Hi-Art System (Tomotherapy Inc.) for intermediate- and high-risk localized prostate cancer (cT1-4N0M0) according to D'Amico's classification at Edogawa Hospital (Tokyo, Japan) (Table I).

The patients were irradiated in a supine position, with a knee support. They were instructed to refrain from urinating for 60–90 minutes before the planning computed tomography (CT) scan and before daily irradiation. They were also encouraged to drink an unspecified volume of water to ensure a clear but tolerable urge to urinate before the planning CT scan and before daily irradiation. They were instructed to take laxatives before the planning CT scan, although no specific instructions were issued regarding bowel movements before daily irradiation.

Table I. Patient characteristics.

	no.
cT stage (TNM 6th ed.)	
1–2a	101(42%)
2b	32 (13%)
2c	40 (16%)
3a	61 (25%)
3b	8 (33%)
4	1 (0.4%)
Gleason score	
2–6	41 (17%)
7	102 (42%)
8–10	100 (41%)
Pretreatment PSA	
0–10	104 (43%)
10–20	67 (28%)
>20	72 (30%)
D'Amico's risk group	
Intermediate	71 (29%)
High	172 (71%)
Neoadjuvant hormone therapy	
No	81 (33%)
Yes	162 (67%)
Mean age (range)	70 (42–85)
Mean prostate volume (range)	21 ml (6–178)
Mean PTV (range)	112 ml (61–273)
Mean bladder volume (range)	235 ml (45–653)

cT stage, clinical tumor stage; PSA, prostate-specific antigen; PTV, planning target volume.

The clinical target volume (CTV) was defined as the prostate that was delineated by the fusion images of CT and magnetic resonance imaging (MRI) with a 5-mm margin and 2 cm of the proximal seminal vesicle. Exceptionally, the whole seminal vesicle was included in the CTV for cases of clinical T3b stage disease. The planning target volume (PTV) was defined as the CTV with a 5-mm margin. The prescribed dose defined as 95% of the PTV receiving ≧100% of the prescription dose (D95) was 76 Gy in 38 fractions. The treatment plans were optimized to satisfy the dose constraints defined by in-house protocols for the PTV and organs at risk (OAR) (Table II). No specific protocols were used for the order of prioritization among the constraints. Cases in which all dose constraints were satisfied were defined as an optimal plan (OP).

We assessed the relationship between the bladder volumes on planning CT and the percentage of patients achieving an OP. Univariate logistic regression analysis was used to examine the predictive value of covariates including clinical T stage (T1–2a, T2b, T2c, T3a, T3b, and T4), Gleason score (2–6, 7, 8–10), pretreatment PSA (0–10, 10–20, and >20), D'Amico's risk group (intermediate or high), neoadjuvant hormone therapy (yes or no), age, PTV, and bladder volume. Those showing significant associations in univariate logistic regression analysis were further tested by multivariate logistic regression analysis.

We used GraphPad Prism version 5 (GraphPad Software Inc.) and SPSS version 17 (IBM) for statistical analysis. Differences were deemed significant when two-tailed p-values were less than 0.05.

Results

Of the subjects, 203 patients (84%) met the definitions for an OP. Among these patients, the mean of

Table II. Dose constraints.

Target/Organ		Dose constraint
PTV	D95	100% (76 Gy)
	Maximum	<110% (83.6 Gy)
	Mean	<105% (79.8 Gy)
Rectum wall*	V40	<65%
	V60	<35%
	V70	<25%
	V78	<10%
Bladder wall	V40	<60%
	V70	<35%
Sigmoid colon	V65	<0.5 ml
Small bowel	V60	<0.5 ml

*Rectum wall within 5 mm above and below the PTV, Vx<y% (or ml) means that no more than y% (or ml) of the volume of the organ receive a dose>x Gy.
PTV, planning target volume.

the mean PTV dose and the maximum dose were 77.4 Gy (range 76.7–79.2 Gy) and 80.7 Gy (range 78.2–83.3 Gy), respectively.

The mean bladder volume (±1 standard deviation; SD) was 266 ml (±130 ml) among those with an OP and 214 ml (±130 ml) among those without an OP ($p = 0.02$, by unpaired t-test).

Logistic regression analysis also showed that bladder volumes below 150 ml decreased the possibility of achieving an OP (Table III). Figure 1 shows the percentage of patients with an OP according to bladder volumes, indicating that the percentage of patients with an OP showed a plateau effect at bladder volumes above 150 ml. On univariate analysis, higher clinical T stage, younger age, treatment with neoadjuvant hormone therapy, and larger bladder volume were predictors for achieving an OP (Table IV). On multivariate analysis, larger bladder volumes ($p = 0.04$), younger age ($p = 0.01$), and higher clinical T stage ($p = 0.03$) were independent predictors for achieving an OP.

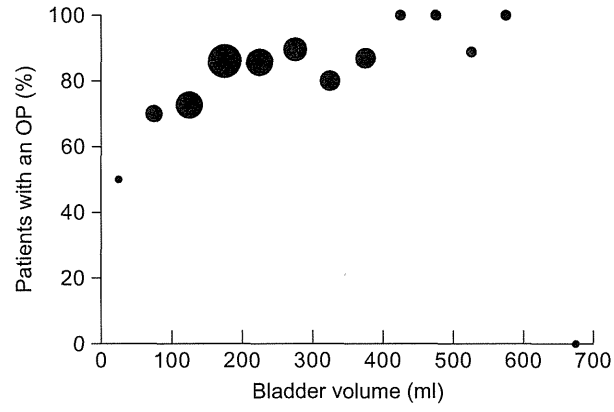

Figure 1. The percentage of patients with an OP according to bladder volume. Patients were divided into subgroups according to their bladder volume by 50 ml. The percentage of patients with an OP was defined by dividing the number of patients with an OP by the number of patients in each subgroup. The size of each dot represents the number in each subgroup.
n, number of patients; OP, optimal plan.

Discussion

We found that bladder volumes among patients with an OP were significantly larger than among patients without an OP. This indicates that bladder volume is a significant factor affecting whether OP is achieved. However, we also found that bladder volumes larger than 150 ml did not contribute to OP rates. We could meet the dose constraints on the bladder even with considerably small bladder volumes. However, small bladders moved the small intestine and the sigmoid colon inside the irradiation field, which made it impossible to meet the dose constraint on those organs. This may explain why we found the plateau effect at bladder volumes above 150 ml.

Table III. Logistic regression analysis between bladder volume and the percentage of patients with an optimal plan.

Bladder volume	Number of patients	Patients with an OP	p	Odds ratio (95% CI)
<100 ml	21	15 (71%)	0.069	0.34 (0.11–1.09)
100–149 ml	34	24 (71%)	0.028	0.33 (0.12–0.89)
150–199 ml	43	37 (86%)	0.761	0.85 (0.29–2.50)
200–249 ml	35	30 (86%)	0.739	0.82 (0.26–2.61)
250–299 ml	27	24 (89%)	0.896	1.10 (0.28–4.31)
>300 ml	83	73 (88%)		1

OP, optimal plan.

Our logistic regression analysis did not show a statistically significant difference in the percentage of patients with an OP in the subgroup with the smallest bladder volume. We think the relatively small number of subjects in the subgroup caused the false negative.

Our results suggested that younger age and higher clinical T stage were also independent predictors for achieving an OP. It is difficult to interpret why age affects OP achievement. There may be some anatomic features among younger patients that make it easier to achieve an OP. It is also difficult to interpret why clinical T stage affects OP achievements although we used the same definition of CTV for all clinical T stages except for the few cases of clinical T3b.

The existence of a clear dose effect for genitourinary (GU) toxicity is well-known in cases in which the entire bladder is irradiated [11]. In the case of prostate irradiation, the cranial portion of the bladder is generally spared, whereas the bladder neck and urethra are irradiated at levels close to the prescribed dose. Most of the published results fails to support a correlation between bladder dose volume histograms (DVH) and GU toxicity [12,13], whereas several studies indicate that the absolute volume of the bladder receiving >78 Gy to 80 Gy is most predictive of late GU toxicity [14,15]. Regarding GU toxicity, a half-full bladder and an empty bladder appear to be acceptable bladder volumes [16]. However, an excessively small bladder volume may move the small intestine and sigmoid colon within the high dose irradiated field [1,4–6]. Therefore, we also imposed dose constraints on the small intestine and sigmoid colon.

Table IV. Univariate logistic regression analysis of association with achieving an optimal plan.

	Patients with an OP (n, 203)	Patients without an OP (n, 40)	p
cT stage (TNM 6th ed.)			0.03
1–2a	77 (38%)	24 (60%)	
2b	26 (13%)	6 (15%)	
2c	35 (17%)	5 (13%)	
3a	57 (28%)	4 (10%)	
3b	7 (3%)	1 (3%)	
4	1 (0.5%)	0 (0%)	
Gleason score			NS
2–6	39 (19%)	2 (5%)	
7	83 (41%)	19 (48%)	
8–10	81 (40%)	19 (48%)	
Pretreatment PSA			NS
0–10	85 (42%)	19 (48%)	
10–20	58 (28%)	9 (23%)	
>20	60 (30%)	12 (30%)	
D'Amico's risk group			NS
Intermediate	60 (30%)	11 (28%)	
High	143 (70%)	29 (73%)	
Neoadjuvant hormone therapy			0.10
No	63 (31%)	18 (45%)	
Yes	140 (69%)	22 (55%)	
Mean age (range)	70 (42–85)	73 (59–83)	0.01
Mean prostate volume (range)	21 ml (6–178)	22 ml (12–103)	NS
Mean PTV (range)	109 ml (61–225)	115 ml (77–273)	NS
Mean bladder volume (range)	266 ml (45–594)	214 ml (48–653)	0.04

cT stage, clinical tumor stage; OP, optimal plan; PSA, prostate-specific antigen; PTV, planning target volume.

Several previous studies have reported that the greatest variation in bladder volume is found in patients with large initial bladder volumes [8,9,17]. Significant variations in bladder volume can confound planned dose distributions. A half-full bladder of 150 ml or slightly larger may represent a reasonable target, offering the potential to improve bladder volume consistency without compromising the dose constraints for the adjacent organs.

A limitation of this investigation is the lack of the clinical correlation. We need to investigate the correlation between bladder volumes on planning CT and clinical outcomes in a future study. In most cases, we use a shrinking PTV if we can not satisfy the dose constraints for OARs. Our concern is that the compromise might cause inferior local control and survival rates. However, long-term follow-up is necessary to clarify the clinical impact. We consider achieving an optimal plan a surrogate marker for clinical outcomes; therefore, we report the correlation between bladder volumes and achieving an optimal plan as the first step.

While optimal bladder volumes vary from institution to institution according to the protocol used, we believe that each institution must seek to recognize what bladder volumes are optimal in definitive radiotherapy for localized prostate cancer.

In conclusions, bladder volume is a significant factor affecting the achieving of an optimal plan. However, our results suggest that bladder volumes exceeding 150 ml may not help meet planning dose constraints.

Acknowledgements

A portion of this report was presented at the 52nd Annual Meeting of the American Society of Therapeutic Radiology and Oncology at San Diego, October 31–November 4, 2010. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] De Meerleer GO, Villeirs GM, Vakaet L, Delrue LJ, De Neve WJ. The incidence of inclusion of the sigmoid colon and small bowel in the planning target volume in radiotherapy for prostate cancer. Strahlenther Onkol 2004;180:573–81.

[2] Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109–22.

[3] Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. Int J Radiat Oncol Biol Phys 1995;31: 1257–80.

[4] Brierley JD, Cummings BJ, Wong CS, McLean M, Cashell A, Manter S. The variation of small bowel volume within the pelvis before and during adjuvant radiation for rectal cancer. Radiother Oncol 1994;31:110–6.
[5] Kim TH, Chie EK, Kim DY, Park SY, Cho KH, Jung KH, et al. Comparison of the belly board device method and the distended bladder method for reducing irradiated small bowel volumes in preoperative radiotherapy of rectal cancer patients. Int J Radiat Oncol Biol Phys 2005;62: 769–75.
[6] Muren LP, Smaaland R, Dahl O. Organ motion, set-up variation and treatment margins in radical radiotherapy of urinary bladder cancer. Radiother Oncol 2003;69: 291–304.
[7] Waldenstrom AC, Alsadius D, Pettersson N, Johansson KA, Holmberg E, Steineck G, et al. Variation in position and volume of organs at risk in the small pelvis. Acta Oncol 2010;49:491–9.
[8] Stam MR, van Lin EN, van der Vight LP, Kaanders JH, Visser AG. Bladder filling variation during radiation treatment of prostate cancer: Can the use of a bladder ultrasound scanner and biofeedback optimize bladder filling? Int J Radiat Oncol Biol Phys 2006;65:371–7.
[9] O'Doherty UM, McNair HA, Norman AR, Miles E, Hooper S, Davies M, et al. Variability of bladder filling in patients receiving radical radiotherapy to the prostate. Radiother Oncol 2006;79:335–40.
[10] Nakamura N, Shikama N, Takahashi O, Ito M, Hashimoto M, Uematsu M, et al. Variability in bladder volumes of full bladders in definitive radiotherapy for cases of localized prostate cancer. Strahlenther Onkol 2010;186:637–42.
[11] Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 1991;21:123–35.
[12] Michalski JM, Winter K, Purdy JA, Wilder RB, Perez CA, Roach M, et al. Preliminary evaluation of low-grade toxicity with conformal radiation therapy for prostate cancer on rtog 9406 dose levels I and II. Int J Radiat Oncol Biol Phys 2003;56:192–8.
[13] Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I. Complications from radiotherapy dose escalation in prostate cancer: Preliminary results of a randomized trial. Int J Radiat Oncol Biol Phys 2000;48:635–42.
[14] Harsolia A, Vargas C, Yan D, Brabbins D, Lockman D, Liang J, et al. Predictors for chronic urinary toxicity after the treatment of prostate cancer with adaptive three-dimensional conformal radiotherapy: Dose-volume analysis of a phase II dose-escalation study. Int J Radiat Oncol Biol Phys 2007; 69:1100–9.
[15] Cheung MR, Tucker SL, Dong L, de Crevoisier R, Lee AK, Frank S, et al. Investigation of bladder dose and volume factors influencing late urinary toxicity after external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2007;67:1059–65.
[16] Fonteyne V, Villeirs G, Lumen N, De Meerleer G. Urinary toxicity after high dose intensity modulated radiotherapy as primary therapy for prostate cancer. Radiother Oncol 2009;92:42–7.
[17] Villeirs GM, De Meerleer GO, Verstraete KL, De Neve WJ. Magnetic resonance assessment of prostate localization variability in intensity-modulated radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2004;60:1611–21.

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(1)53–57
doi:10.1093/jjco/hyr175
Advance Access Publication 30 November 2011

Patterns of Practice in Intensity-modulated Radiation Therapy and Image-guided Radiation Therapy for Prostate Cancer in Japan

Katsumasa Nakamura[1,*], Tetsuo Akimoto[2], Takashi Mizowaki[3], Kazuo Hatano[4], Takeshi Kodaira[5], Naoki Nakamura[6], Takuyo Kozuka[7], Naoto Shikama[8] and Yoshikazu Kagami[9]

[1]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, [2]Department of Radiation Oncology and Particle Therapy, National Cancer Center Hospital East, Kashiwa, [3]Department of Radiation Oncology and Image-applied Therapy, Kyoto University Graduate School of Medicine, Kyoto, [4]Division of Radiation Oncology, Chiba Cancer Center, Chiba, [5]Department of Radiation Oncology, Aichi Cancer Center, Nagoya, [6]Department of Radiation Oncology, St Luke's International Hospital, Tokyo, [7]Department of Radiation Oncology, The Cancer Institute, Ariake Hospital of Japanese Foundation for Cancer Research, Tokyo, [8]Department of Radiation Oncology, Saitama Medical University International Medical Center, Saitama and [9]Department of Radiology, Showa University School of Medicine, Tokyo, Japan

*For reprints and all correspondence: Katsumasa Nakamura, Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail: nakam@radiol.med.kyushu-u.ac.jp

Received September 15, 2011; accepted November 4, 2011

Background: The purpose of this study was to compare the prevalence of treatment techniques including intensity-modulated radiation therapy and image-guided radiation therapy in external-beam radiation therapy for prostate cancer in Japan.
Methods: A national survey on the current status of external-beam radiation therapy for prostate cancer was performed in 2010. We sent questionnaires to 139 major radiotherapy facilities in Japan, of which 115 (82.7%) were returned.
Results: Intensity-modulated radiation therapy was conducted at 67 facilities (58.3%), while image-guided radiation therapy was conducted at 70 facilities (60.9%). Simulations and treatments were performed in the supine position at most facilities. In two-thirds of the facilities, a filling bladder was requested. Approximately 80% of the facilities inserted a tube or encouraged defecation when the rectum was dilated. Some kind of fixation method was used at 102 facilities (88.7%). Magnetic resonance imaging was routinely performed for treatment planning at 32 facilities (27.8%). The median total dose was 76 Gy with intensity-modulated radiation therapy and 70 Gy with three-dimensional radiation therapy. The doses were prescribed at the isocenter at the facilities that conducted three-dimensional radiation therapy. In contrast, the dose prescription varied at the facilities that conducted intensity-modulated radiation therapy. Of the 70 facilities that could perform image-guided radiation therapy, 33 (47.1%) conducted bone matching, 28 (40.0%) conducted prostate matching and 9 (12.9%) used metal markers. Prostate or metal marker matching tended to produce a smaller margin than bone matching.
Conclusions: The results of the survey identified current patterns in the treatment planning and delivery processes of external-beam radiation therapy for prostate cancer in Japan.

Key words: radiation therapy – urologic-radoncol – radiation oncology

INTRODUCTION

External beam radiation therapy (EBRT) has developed rapidly in recent years (1,2) and treatment equipment with which intensity-modulated radiation therapy (IMRT) and/or image-guided radiation therapy (IGRT) can be conducted are being introduced into Japan (3). IMRT and IGRT are particularly useful in EBRT for prostate cancer and are routinely used in the USA (4) and recommended in worldwide guidelines (5,6).

In Japan, IMRT and IGRT were listed as eligible for insurance reimbursement in 2008 and 2010, respectively. However, the present situation regarding the use of these techniques in EBRT for prostate cancer remains unclear (7,8). Therefore, we conducted a survey that would clarify the operational situation, treatment planning and treatment processes of IMRT and/or IGRT when used in EBRT for prostate cancer.

PATIENTS AND METHODS

In February 2010, we sent a questionnaire on EBRT for prostate cancer to 139 major facilities including university hospitals, cancer centers and designated prefectural cancer centers and hospitals. The questionnaire was also sent to the hospitals which had treatment machines with IGRT functions, including Novalis (BrainLAB, Heimstetten, Germany), Tomotherapy (Accuray Inc., Sunnyvale, USA) and MHI-TM2000 (Mitsubishi Heavy Industries, Ltd., Nagoya, Japan).

The survey was composed of categories regarding treatment planning, dose fractionation and methods of implementation of EBRT for prostate cancer. If methods differed according to the type of radiation techniques used such as three-dimensional radiation therapy (3DCRT) or IMRT, we required responses regarding the most precise radiation method presently used. Among the 139 facilities to which we sent the survey, 115 (82.7%) gave responses, which were then analyzed. The high response rate allowed an extensive and representative data analysis.

RESULTS

General Information

Figure 1 shows the distribution of the number of patients with prostate cancer treated with EBRT at facilities in 2009 over the course of 1 year. There were 30 facilities (26.1%) at which over 50 patients were treated in 1 year. Of the 115 total facilities, 67 (58.3%) conducted IMRT, 70 (60.9%) conducted IGRT and 58 (50.4%) conducted both.

Treatment Planning

Figure 2 shows the condition of the bladder at the treatment planning stage and during the treatment. In approximately

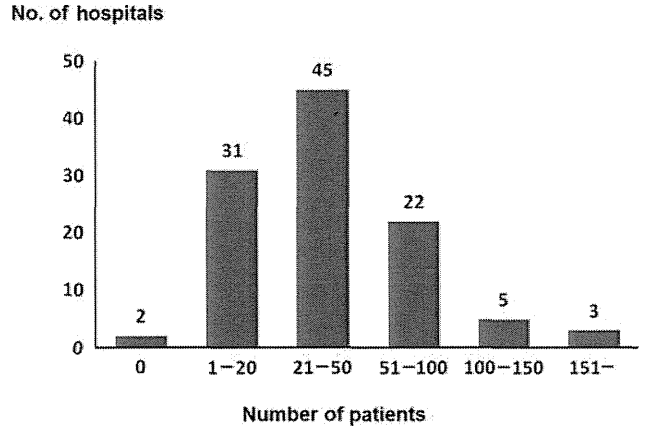

Figure 1. Total number of patients with prostate cancer treated with external-beam radiation therapy at facilities in 2009. Because some data were missing, the total numbers of patients were less than the actual number.

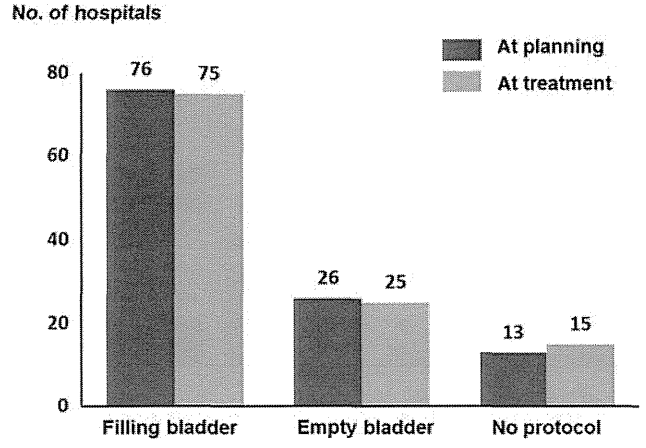

Figure 2. Condition of the bladder at the treatment planning stage and during treatment.

two-thirds of the facilities, a filling bladder was requested. The time spent pooling urine was 1 h at 56 facilities (48.7%), 1–2 h at 8 facilities (7.0%) and 30 min at 7 facilities (6.1%). Seven facilities (6.1%) also asked patients to drink water prior to treatment.

Figure 3 shows the condition of the rectum. Approximately 80% of the facilities inserted a tube or encouraged defecation when the rectum was dilated. Laxative medication was used at one-quarter of the facilities.

Simulations and treatments were performed in the supine position at 105 facilities (91.3%) and the prone position at 10 facilities (8.7%). Figure 4 shows methods of patient fixation. Some kind of fixation method was used at 102 facilities (88.7%). Although various methods were reported, a vacuum cushion, thermoplastic shell and foot support were used most frequently.

Magnetic resonance imaging (MRI) was routinely performed for treatment planning at 32 facilities (27.8%). Of these, 15 facilities (13.0%) performed computed tomography

(CT)-MRI image fusion with treatment planning software. MRI taken at the time of diagnosis was used as a reference at 66 facilities (57.4%), while 17 facilities (14.8%) did not use MRI for treatment planning.

Treatment

Radiation therapy was carried out with 2 Gy per fraction at 100 facilities (86.9%), 2.1–3 Gy at 14 facilities (12.2%) and 1.8 Gy at 1 facility (0.9%). Most facilities conducted treatment five times a week. Treatment was conducted three times a week at five facilities (4.3%) and four times a week at three facilities (2.6%).

Figure 5 shows the distributions of radiation doses delivered to the prostate at facilities using a fraction dose of 2 Gy. The median total dose was 76 Gy with IMRT and 70 Gy with 3DCRT. The doses were prescribed at the isocenter at the facilities that conducted 3DCRT. In contrast, the dose prescription varied greatly at the facilities that conducted IMRT. Of the 67 facilities that conducted IMRT, D95, which is the minimum absorbed dose that covers 95% of the planning target volume (PTV), was used as a dose prescription at 24 facilities (35.8%). A dose prescription requiring that 95% of the prescribed isodose line cover 95% of the PTV was used at 4 facilities (6.0%), the mean PTV dose was used at 13 facilities (19.4%) and other methods at 26 facilities (38.8%).

The most popular IGRT methods (54 facilities) involved 2D matching with X-ray fluoroscopy or 3D matching with a flat-panel cone-beam CT. Eight facilities used CT on rail and 4 facilities used ultrasonic devices. Of the 70 facilities that could perform IGRT, 33 (47.1%) conducted bone matching, 28 (40.0%) conducted prostate matching and 9 (12.9%) used metal markers. At the treatment of prostate cancer, 60 facilities (85.7%) always conducted IGRT, while 9 (12.9%) conducted IGRT at regular intervals.

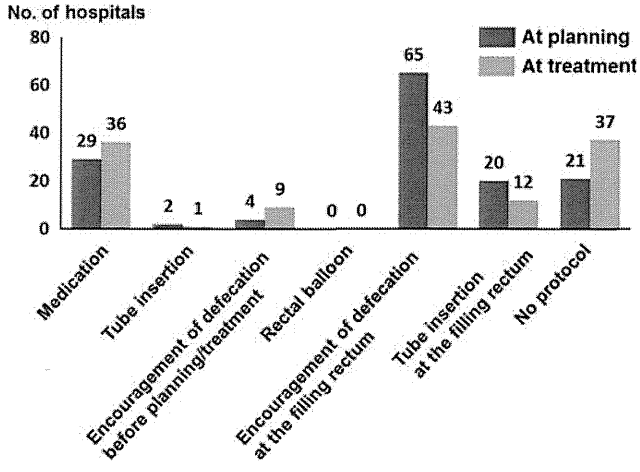

Figure 3. Condition of the rectum at the treatment planning stage and during treatment. Multiple answers allowed.

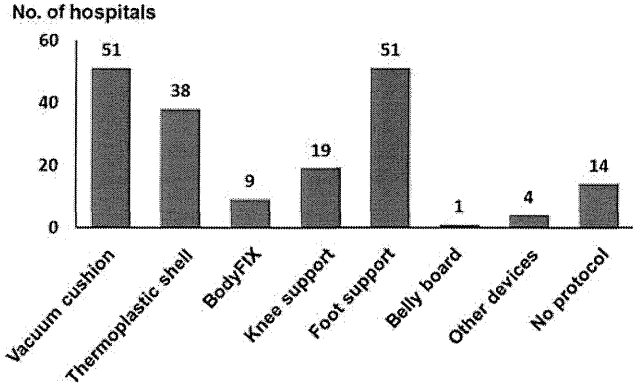

Figure 4. Fixation of the patients at the treatment planning stage and during treatment. Multiple answers allowed.

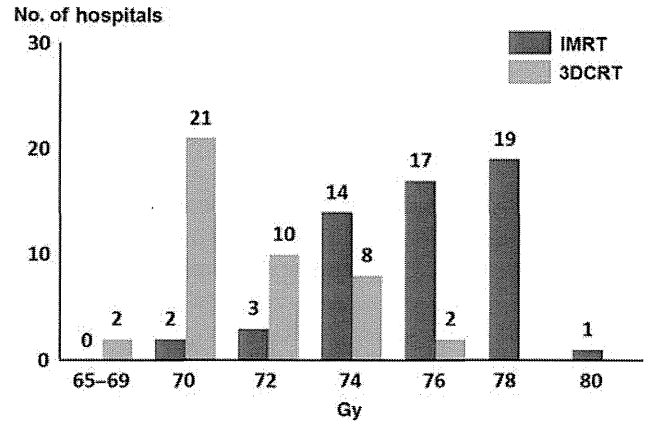

Figure 5. Total dose to the prostate.

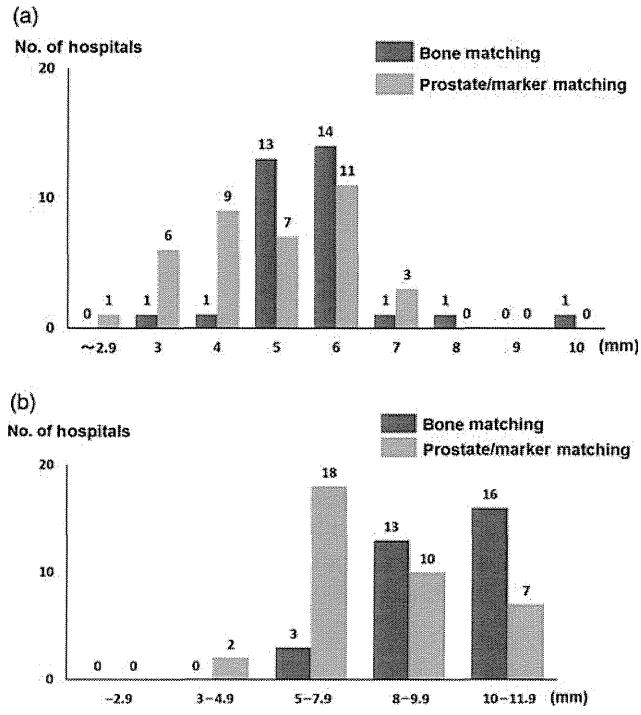

Figure 6. Margins from the prostate to planning target volume for patients with T1–2 tumors treated with IGRT: (a) rectal side and (b) other sides.

Figure 6 show the distribution of the prostate-PTV margins for patients with typical T1–2 tumors treated with IGRT. Prostate or metal marker matching tended to produce slightly smaller margins than bone matching.

DISCUSSION

This study provides a clear picture of present practices of IMRT and/or IGRT for prostate cancer in Japan.

Simulations and treatments were performed in the supine position at most facilities. However, facilities employed various fixation methods. In most facilities, some kind of fixation method was used, although immobilization devices for body malignancies are not covered by health insurance in Japan. In the patterns of care study on prostate cancer patients who were treated with EBRT from 2003 to 2005, immobilization devices were used on only 15% of patients (7). One reason for the high frequency of the usage of patient immobilization devices in this study could be the gradual popularization of fixation methods over time. An additional reason is probably the fact that some sort of fixation method tends to be used in more precise radiation treatment, because patient immobilization can be an important contributor to the reproducibility and accuracy of radiotherapy (9).

The pretreatment condition of the bladder and rectum also varied greatly among facilities. Although fixation of the prostate is frequently conducted with a rectal balloon in Western countries (10), this method has not been used at all in Japan.

In this study, we did not investigate PTV margins when IGRT was not used. Therefore, we were unable to clarify whether IGRT causes decreased margins. However, PTV margins tended to be slightly smaller with prostate or fiducial marker matching than that with bone matching. PTV margins should be determined at each facility taking into account position errors caused not only by the IGRT method, but also by the patient position, fixation method and pretreatment condition of the bladder and rectum. Enmark et al. (11) demonstrated that a margin of 4 mm in all directions was adequate to account for uncertainties including the inter- and intrafraction motions, if IGRT with fiducial markers is performed on a daily basis. Some facilities have chosen prostate-PTV margins of <4 mm. Because of uncertainties such as intrafraction motion or uncertainty of the target delineation, decreases in the PTV margin should be carefully performed even when IGRT is applied.

The radiation dose administered at most facilities was 2 Gy per fraction. The median value of the total radiation dose was 76 Gy with IMRT and 70 Gy with 3DCRT. It is well known that the radiation dose is a strong independent predictor of failure (12), and IMRT can reduce the unwanted doses to nearby organs at risk. Therefore, as IMRT becomes more widespread in Japan, more appropriate higher dosages of radiation should be utilized. However, a significant problem is the fact that the IMRT dose prescription varies. It is necessary to define and develop recommended guidelines for dose prescription and a dose reporting system for IMRT in Japan (13).

IMRT and IGRT were being conducted at approximately half of the facilities in this study. However, our survey targeted large-scale facilities. If all radiation therapy facilities in Japan were to be surveyed, this proportion would probably be smaller (3). At present, high-precision radiation therapy devices such as IMRT and IGRT are being rapidly introduced (3,14), and an increasing number of facilities will surely come to adopt IMRT and IGRT. The results of the survey in this study will provide beneficial information to those facilities as they begin treatment.

Acknowledgements

We thank all radiation oncologists who participated in this study. We are also grateful to Y. Asazawa for making the questionnaire available to us.

Funding

This study was supported in part by Grant-in Aid from the Ministry of Health, Labor and Welfare of Japan [H21–018].

Conflict of interest statement

None declared.

References

1. Harmenberg U, Hamdy FC, Widmark A, Lennernas B, Nilsson S. Curative radiation therapy in prostate cancer. *Acta Oncol* 2011;50(Suppl 1):98–103.
2. Ghilezan M, Yan D, Martinez A. Adaptive radiation therapy for prostate cancer. *Semin Radiat Oncol* 2010;20:130–7.
3. Teshima T, Numasaki H, Shibuya H, Nishio M, Ikeda H, Sekiguchi K, et al. Japanese structure survey of radiation oncology in 2007 based on institutional stratification of patterns of care study. *Int J Radiat Oncol Biol Phys* 2010;78:1483–93.
4. Kupelian P, Meyer JL. Image-guided, adaptive radiotherapy of prostate cancer: toward new standards of radiotherapy practice. *Front Radiat Ther Oncol* 2011;43:344–68.
5. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer V1 2011. http://www.nccn.org/.
6. Horwich A, Parker C, Kataja V. Prostate cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;20(Suppl 4):76–8.
7. Nakamura K, Ogawa K, Sasaki T, Onishi H, Koizumi M, Araya M, et al. Patterns of radiation treatment planning for localized prostate cancer in Japan: 2003–05 patterns of care study report. *Jpn J Clin Oncol* 2009;39:820–4.
8. Ogawa K, Nakamura K, Sasaki T, Onishi H, Koizumi M, Araya M, et al. Radical external beam radiotherapy for clinically localized prostate cancer in japan: changing trends in the patterns of care process survey. *Int J Radiat Oncol Biol Phys* 2011, in press.
9. Fiorino C, Reni M, Bolognesi A, Bonini A, Cattaneo GM, Calandrino R. Set-up error in supine-positioned patients immobilized

with two different modalities during conformal radiotherapy of prostate cancer. *Radiother Oncol* 1998;49:133–41.
10. Smeenk RJ, Teh BS, Butler EB, van Lin EN, Kaanders JH. Is there a role for endorectal balloons in prostate radiotherapy? A systematic review. *Radiother Oncol* 2010;95:277–82.
11. Enmark M, Korreman S, Nystrom H. IGRT of prostate cancer; is the margin reduction gained from daily IG time-dependent? *Acta Oncol* 2006;45:907–14.
12. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009;74:1405–18.
13. ICRU. International Commission on Radiation Units and Measurements. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). Report 83. Oxford: Oxford University Press 2010.
14. Teshima T, Numasaki H, Shibuya H, Nishio M, Ikeda H, Ito H, et al. Japanese structure survey of radiation oncology in 2005 based on institutional stratification of patterns of care study. *Int J Radiat Oncol Biol Phys* 2008;72:144–52.

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation: Breast Cancer

Identifying Patients Who Are Unsuitable for Accelerated Partial Breast Irradiation Using Three-Dimensional External Beam Conformal Techniques

Naoto Shikama, M.D.,* Naoki Nakamura, M.D.,† Naoaki Kunishima, M.D.,† Shogo Hatanaka, M.S.,† and Kenji Sekiguchi, M.D.†

**Department of Radiation Oncology, Saitama Medical University International Medical Center, Saitama, Japan; and †Department of Radiation Oncology, St. Luke's International Hospital, Tokyo, Japan*

Received Mar 4, 2011, and in revised form Dec 27, 2011. Accepted for publication Dec 29, 2011

Summary

Fifty consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) accelerated partial breast irradiation (APBI) techniques. Dose–volume histogram (DVH) constraints were satisfied in 20% of patients with a long cranio-caudal surgical clip distance (CCD; ≥5.5 cm) and 92% of those with a short CCD ($p <$ 0.0001). Patients with long CCDs might be unsuitable for 3D-CRT APBI due to nonoptimal DVH constraints.

Purpose: Several recent studies reported that severe late toxicities including soft-tissue fibrosis and fat necrosis are present in patients treated with accelerated partial breast irradiation (APBI) and that these toxicities are associated with the large volume of tissue targeted by high-dose irradiation. The present study was performed to clarify which patients are unsuitable for APBI to avoid late severe toxicities.

Methods and Materials: Study subjects comprised 50 consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery, and in whom five or six surgical clips were placed during surgery. All patients were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) APBI techniques according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39 and Radiation Therapy Oncology Group (RTOG) 0413 protocol. The beam arrangements included mainly noncoplanar four- or five-field beams using 6-MV photons alone.

Results: Dose–volume histogram (DVH) constraints for normal tissues according to the NSABP/RTOG protocol were satisfied in 39 patients (78%). Multivariate analysis revealed that only long craniocaudal clip distance (CCD) was correlated with nonoptimal DVH constraints ($p = 0.02$), but that pathological T stage, anteroposterior clip distance (APD), site of ipsilateral breast (IB) (right/left), location of the tumor (medial/lateral), and IB reference volume were not. DVH constraints were satisfied in 20% of patients with a long CCD (≥5.5 cm) and 92% of those with a short CCD ($p < 0.0001$). Median IB reference volume receiving ≥50% of the prescribed dose (IB-V_{50}) of all patients was 49.0% (range, 31.4–68.6). Multivariate analysis revealed that only a long CCD was correlated with large IB-V_{50} ($p < 0.0001$), but other factors were not.

Conclusion: Patients with long CCDs (≥5.5 cm) might be unsuitable for 3D-CRT APBI because of nonoptimal DVH constraints and large IB-V_{50}. © 2012 Elsevier Inc.

Keywords: Partial breast irradiation, Breast cancer, Radiotherapy, 3D-conformal radiotherapy, Toxicity

Reprint requests to: Naoto Shikama, M.D., Department of Radiology Oncology, Saitama Medical University International, Medical Center, 1397-1 Yamane, Hidaka-City, Saitama, 350-1298 Japan. Tel: +81-42-984-4111; Fax: +81-42-984-4136; E-mail: nshikama0525@gmail.com

Presented in part at the 52th Annual Meeting of the American Society for Radiology Oncology, San Diego, CA, in October 2010.

Supported by Health and Labor Sciences Research Grants (H21-018, H22-001), Grants-in-Aid for Cancer Research (20S-5), and Grants-in-Aid for Scientific Research: "Third term comprehensive control research for cancer (H22-043)" from the Ministry of Health, Labor, and Welfare of Japan.

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. e313–e318, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.12.091

Introduction

Breast-conserving therapy including partial resection and postoperative whole breast irradiation has constituted standard care for patients with early breast cancer (1). Some Phase III trials of postoperative radiotherapy and systematic reviews have revealed that omission of postoperative radiotherapy increases recurrence in breasts by threefold, and increases absolute breast cancer mortality by more than 5% (1, 2). Several reasons, including the long-term radiation schedule, level of surgeon involvement in the radiation decision, patient refusal, and comorbidity, lead to omission of postoperative radiotherapy. In fact, approximately 25% of patients who underwent conservative surgery did not receive postoperative radiotherapy in the United States (1991–2002) (3).

Approximately 85% of breast recurrences after breast conservative therapy develop in the vicinity of the tumor bed; several percent appear "elsewhere" in the breast, and the absolute number of such failures is very low (4). In the past decade, prospective clinical trials and retrospective studies evaluated the efficacy and safety of accelerated partial breast irradiation (APBI) using small radiation fields and a large fraction size. These studies reported good treatment outcome and minimal late toxicities after a short follow-up duration (4–6). However, two recent studies reported that the large volume of irradiated breast tissue was correlated with higher incidences of late severe toxicities including soft-tissue fibrosis and fat necrosis of the breast, which were clearly associated with marked cosmetic compromise (7, 8). Appropriate eligibility criteria and treatment schedules for APBI should be established to avoid late severe toxicities. The present study aimed to identify patients who are unsuitable for APBI because of the potential risk of late toxicities including soft-tissue fibrosis and fat necrosis after APBI using three-dimensional conformal radiotherapy (3D-CRT).

Methods and Materials

Patients

The study population consisted of 50 consecutive patients with unilateral breast cancer, at Union for International Cancer Control 7th Stage 0–II, who received breast-conserving therapy between April 2009 and September 2009. Median patient age was 49 years (range, 33–73). The right-to-left ratio of the ipsilateral breast (IB) was 25:25, and the medial-to-lateral ratio of the tumor location was 19:31. All patients underwent partial breast resection, and five or six surgical clips were placed at the borders of the surgical bed. Thirty-one patients had pathological T stage 1 (pT1), 7 patients had pT2, and 12 patients had pTis. Sentinel node biopsy and/or axillary node dissection revealed that 47 patients had pathological N stage 0 (pN0), and 2 patients had pN1. pN stage was not evaluated for 1 patient.

Radiation treatment planning

All patients were placed in the supine position and underwent computed tomography (CT) as part of the standard planning for whole breast irradiation. CT scanning was performed using a 2-mm thick-slice and a slice step of 2 mm; slices extended to completely cover the bilateral whole breast, lung, heart, thyroid, and a 5-cm margin in the cranial and caudal directions. No respiratory control was used. The following structures were contoured for the planning of 3D-CRT: surgical clips, clinical target volume (CTV), planning target volume (PTV), ipsilateral whole breast (IB) reference, IB reference excluding PTV (IB-PTV), contralateral breast, heart, bilateral lungs, and thyroid. To keep the probability of comparison consistent with outcomes of other studies, the contouring of IB reference was made up using an automated contouring method applied by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-39) and Radiation Therapy Oncology Group (RTOG 0413) protocol (9). CTV was defined as the volume bound by uniform expansion of surgical clips by 1.5 cm in all dimensions, excluding the pectoralis muscles, chest wall, lung, heart, pericardial fat, and 5 mm beneath the skin (9). PTV was defined as the volume bound by uniform expansion of CTV by 1.0 cm in all dimensions. PTV_EVAL, the volume for dose–volume histogram (DVH) analysis, was defined as the volume of PTV excluding the first 5 mm of tissue under the skin, the posterior breast tissue extent (chest wall and pectoral muscles), lung, heart, and pericardial fat.

All 50 patients were replanned using 3D-CRT planning system software (Pinnacle^3 version 8.0m, Pinnacle Treatment System; Philips, Milpitas, CA). To correctly evaluate heterogeneous tissue density, the convolution algorithm was used. The NSABP B-39/RTOG 0413 protocol dose limitation was used as a guideline for specified normal tissue constraints (9). Beam arrangements included noncoplanar mainly four- or five-field beams using 6-MV photons referring to the method reported by Vicini *et al.* (10). No electron beam was used. The exertion of simulation planning was for minimizing doses to organs at risk, and improving a homogeneous dose to the target volume. Beam weights, beam angle, and wedge angles were manually optimized, such that the targeted goal was to cover $\geq$90% of the PTV_EVAL by a dose $\geq$90% of the prescribed dose (9). The DVH constraints adopted for plan optimization are shown in Table 1.

A total dose of 30 Gy in five fractions was prescribed to the International Commission on Radiation Units and Measurements 50 reference point dose (isocenter) (11). The isocenter was placed in the center of the PTV. This treatment schedule was proposed by the Department of Radiation Oncology at New York University using the prone position and parallel-opposed minitangents external beam therapy (12). The New York University study demonstrated that this abbreviated regimen was well tolerated, with only mild acute adverse events and excellent or good cosmetic outcome. However, given the typical Japanese woman's breast size and shape, we had patients assume a supine position and used a noncoplanar three-, four-, five-, and six-beam technique.

Data analysis

IB volume, target volumes, and distance of surgical clips were measured by CT images on the radiation treatment planning (RTP) system. The craniocaudal surgical clip distance (CCD) was defined as the longitudinal distance along the body axis between head-side clip and foot-side clip, and the anteroposterior surgical clip distance (APD) was defined as the vertical distance between anterior-side clip and posterior-side clip. The IB reference volume receiving 50% of the prescribed dose (IB-V_{50}) was calculated. The homogeneity index (HI) was defined as the ratio of maximum dose

Table 1 DVH constraints for planning

IB reference	≤60%	≥50% of the prescribed dose	IB-V50 ≤60%
	≤35%	≥100% of the prescribed dose	IB-V100 ≤35%
Contralateral breast	Any point	≤3% of the prescribed dose	0.9 Gy
Ipsilateral lung	≤15%	≥30% of the prescribed dose	V30 ≤15%
Contralateral lung	≤15%	≥5% of the prescribed dose	V5 ≤15%
Heart			
Right-sided lesions	≤5%	≥5% of the prescribed dose	V5 ≤5%
Left-sided lesions	≤40%	≥5% of the prescribed dose	V5 ≤40%
Thyroid	Any point	≤3% of the prescribed dose	0.9 Gy

Abbreviations: DVH = dose–volume histogram; IB = ipsilateral breast.

of PTV_EVAL to minimum dose of PTV_EVAL. The conformity index (CI) was defined as the ratio of volume that was covered by the minimal dose of PTV_EVAL to the volume of PTV. The associations between categorical variables (*e.g.*, site of IB) and patient and tumor characteristics at baseline were analyzed using Fisher's two-tailed exact test. Statistically significant differences between two sample means and medians for continuous variables (*e.g.*, IB reference volume) were analyzed using the Student's unpaired *t*-test. A p value of less than 0.05 was considered statistically significant. Multivariate analysis of prognostic factors was performed with the Cox proportional hazards model. Statistical analyses were performed with JMP software, version 5.1 (SAS Institute, Cary, NC).

Results

Outcome of 3D-CRT planning

Median IB reference volume of all patients was 824 cm^3 (range, 425–1868) (Table 2). Median right IB reference volume was 794 cm^3 (range, 463–1556) and the left IB reference volume was 849 cm^3 (range, 425–1868), respectively ($p = 0.63$). Median CCD and APD for all patients were 4.5 cm (range, 2.0–9.5) and 4.2 cm (range, 0.8–7.6), respectively.

Median CTV for all patients was 56.3 cm^3 (range, 11.3–83.6), and median PTV for all patients was 246.9 cm^3 (range, 113.4–370.9) (Table 3). The median ratio between IB-PTV and IB reference volume was 74.9% (range, 54.0–86.9). The number of external beams ranged from three to six; the four-beam technique was mainly used for patients with the right breast region, and the five-beam technique was mainly used for patients with the left breast region. The median value of mean dose of PTV_EVAL was 30.2 Gy (range, 29.5–30.8). The median value of HI for all patients was 1.24 (range, 1.14–1.39), and the median value of CI for all patients was 1.38 (range, 1.01–2.40).

Unsuitable patients for the NSABP B-39/RTOG 0413 protocol

DVH constraints for organs at risk according to the NSABP B-39/RTOG 0413 protocol were satisfied in 39 patients (78%). Seven patients showed nonoptimal DVH for the ipsilateral lung; 5 patients for the contralateral breast; 4 patients for IB-V_{50}; 2 patients for the heart; and 1 patient for the thyroid. Univariate logistic regression analysis revealed that long CCD and medial tumors were correlated with nonoptimal DVH constraints ($p < 0.0001$ and $p = 0.007$, respectively), but pathological T stage excluding pTis (T1a/T1b/T1c/T2), APD, site of IB (right/left), and IB reference volume were not ($p = 0.98$, $p = 0.54$, $p = 0.73$, and

Table 2 Patients characteristics

				Univariate analysis
	All patients ($n = 50$)	Optimal DVH ($n = 39$)	Nonoptimal DVH ($n = 11$)	p value
Pathological T stage				
pTis/pT1/pT2	12/31/7	10/24/5	2/7/2	0.82
pT1a/pT1b/pT1c/pT2*	5/5/20/7	4/4/15/5	1/1/5/2	0.98
Site of IB				
Right/left	25/25	20/19	5/6	0.73
Location of tumor				
Mediolateral	19/31	11/28	8/3	0.007
IB reference volume (cm^3)				
Median (range)	824 (425–1868)	828 (425–1868)	725 (528–1032)	0.10
CCD (cm)				
Median (range)	4.5 (2.0–9.5)	3.5 (2.0–5.5)	6.0 (4.5–9.5)	<0.0001
APD (cm)				
Median (range)	4.2 (0.8–7.6)	4.2 (0.8–7.6)	4.6 (1.0–7.5)	0.54

Abbreviations: APD = anteroposterior clip distance; CCD = craniocaudal clip distance; DVH = dose–volume histogram; IB = Ipsilateral breast.
* 1 patient was not classified according to subcategory of pathological T stage.