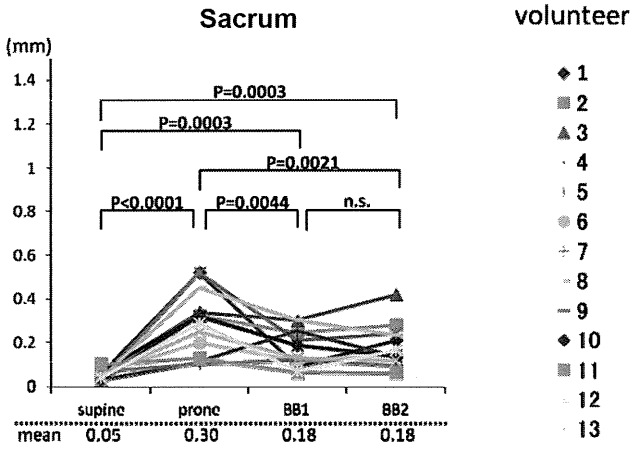


Figure 4: The distribution of the standard deviation of points of interest for the 13 volunteers. Levels of significance are displayed. Means of the standard deviations for each POIs are listed below. Abbreviation: n.s. = Not significant.

surface of the prostate, the tip of the seminal vesicle, and the sacrum. Comparing the BB1 position with the BB2 position, there were no significant differences in any of the POIs.

Discussion

A belly board has been used frequently to reduce the bowel dose during pelvic irradiation. Koelbl *et al.* (9) studied the effect of using the prone position with a belly board in 20 rectal cancer patients treated with postoperative pelvic radiotherapy. They reported that the irradiated small bowel volume was smaller in the prone position than in the supine position, and that the use of the prone position combined with the belly board reduced the irradiated volume within the PTV by 54%. Das *et al.* (8) performed a dose-volume analysis on the effect of a belly board on small bowel irradiation in 12 patients with rectal cancer who were treated with pelvic radiotherapy. They reported that using the belly board significantly reduced the irradiation volume at all dose levels between 10 and 100%. However, to our knowledge, there were no studies on the influence of the belly board on organ motion. This study clearly shows that respiratory-induced prostate motion in the prone position is significantly reduced by using a belly board.

Prostate movement induced by respiration is considered to be related to intra-abdominal pressure, which is produced by the motion of the abdominal contents within the confined space of the pelvis (2). However, if the belly board is used in the prone position, the abdominal tissues/organs that are ordinarily displaced downwards by inspiration could shift into the space of the belly board. As a result, prostate motion may be reduced in the prone position using the belly board.

Koelbl *et al.* (11) also reported on the influence of different patient positions on the radiation dose in the small bowel when a belly board is used. In their study, the patients were placed in three different positions relative to the belly board. The lower edge of the opening of the belly board was near the symphysis, the lower end of the sacroiliac joints and the lumbosacral junction. When the lower edge of the opening was placed near the lumbosacral junction, the volume of the small bowel that was irradiated was at its lowest. In the present study, belly board positions were not significantly related to the amount of respiratory-induced motion in the prostate. As for the respiratory-induced motion, it seems that the position of the belly board did not have any significant influence on the motion of the prostate. This may be in part because the respiratory-induced motion in the prone position decreases simply because of the decrease in intra-abdominal pressure made possible by the space afforded by the belly board.

In previous reports, intrafraction prostate motion has been measured using implanted radiopaque markers (2-4, 12, 13), and was found to be minimal in the supine position. Cheung *et al.* (12) measured the intrafraction prostate motion in pretreatment and post-treatment portal images in 33 patients with implanted markers. The patients were in the supine position, and a custom vacuum lock bag was used for immobilization. They showed that the prostate motion was less than 1 mm in all directions. Meanwhile, respiratory-induced prostate motion was substantial in the prone position (2-4). Kitamura *et al.* (4) reported that the amplitude of intrafraction motion in the supine position was statistically smaller in all directions than that in the prone position. These tests used a fluoroscopic, real-time tumor-tracking system to image a fiducial marker within the prostate. Recently, the real-time motion in the prostate in the supine and/or prone positions has been demonstrated using cine-MRI (14-17). Cine-MRI enables accurate and realistic representations of the motion in the prostate and surrounding tissues/organs. However, the deficit of cine-MRI in evaluating respiratory movement is because the images were recorded every one second strictly, the acquired images did not completely fit the breathing cycle. In order to clear this deficit, we compared maximum ranges and SDs in this study. Ghilezan *et al.* (16) assessed intrafractional prostate gland motion with cine-MRI. The images in their study were acquired during the 1 h MRI session at 6-s intervals. They divided into 2 groups according to rectal filling status: full- vs. empty-rectum. The displacement of eleven POIs (standard deviation) ranged from 0.98 to 1.72 mm for the full-rectum group and from 0.68 to 1.04 mm for the empty-rectum group. The reason of their SDs resulting in larger than the present study is considered because the intrafractional movement during 1 h MRI session might include other factors, such as rectal movement and change of muscle tension, which may possibly be larger than respiratory-induced motion. In the present study, cine frames were acquired every second, allowing more realistic imaging of the prostate motion in relation to respiration. Therefore, respiratory-induced motion could be detected in the supine and prone positions with or without a belly board.

The selection of treatment position is a critical choice in radiation therapy. The published literature demonstrating the efficacy of three-dimensional conformal radiotherapy for prostatic cancer shows considerable variation in the use of the prone and supine positions. The choice of position can alter the external contour of the treated area and has the potential to alter the spatial relationship between internal organs. In this report, respiratory-induced prostate motion was significantly larger in the prone position than in the supine position, although reduced prostate motion was shown in the prone position with a belly board. For respiratory-induced motion at least, the supine position is considered to be more favorable for prostatic irradiation.

There were several limitations in this study. First, we did not use immobilization devices that may have affected respiratory movement. Malone *et al.* (2) reported that significant prostate movement can be induced by respiration when patients are immobilized in thermoplastic shells. Therefore, immobilization using a belly board may increase prostate motion. Second, only POIs in the mid-sagittal plane were used. Thus, movement on the lateral side was not considered in this study. In previous reports (13, 14, 18, 19), intrafraction motion of the prostate was found to be greater in the anteroposterior and superoinferior dimensions than in the left-right dimension. By inference from these reports, it was considered that lateral movement would not be large, even when the patients were treated in the prone position. Third, although our study showed that respiratory-induced prostate motion in the prone position was reduced by using a belly board, this is only one of the components to consider. Another potential source of intrafraction prostate motion may be rectal or bladder filling status, patient pelvic musculature changes and abrupt movement. The magnitude of the intrafraction organ motions caused by these factors will also have a strong impact on the definition of margins.

In conclusion, our data demonstrated that respiratory-induced prostate motion was significantly larger in the prone position than in the supine position, although motion in the prone position could be to some extent reduced by using a belly board. Therefore, if the prone position is chosen for prostate cancer radiotherapy, the use of a belly board should be considered.

Conflict of Interest

It is hereby certified that none of the authors have any financial or other dealings that could lead to a conflict of interest.

Acknowledgments

This study was supported in part by KAKENHI (Nos. 18209040, 23390302, and 20284507) and a Health Labor Sciences Research Grant from the Japanese Ministry of Health, Labor and Welfare.

References

1. Zelefsky, M. J., Crean, D., Mageras, G. S., Lyass, O., Happersett, L., Ling, C. C., Leibel, S. A., Fuks, Z., Bull, S., Kooy, H. M., van Herk, M., Kutcher, G. J. Quantification and predictors of prostate position variability in 50 patients evaluated with multiple CT scans during conformal radiotherapy. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology 50*, 225-234 (1999). DOI: 10.1016/S0167-8140(99)00011-0
2. Malone, S., Crook, J. M., Kendal, W. S., Szanto, J. Respiratory-induced prostate motion: quantification and characterization. *International Journal of Radiation Oncology, Biology, Physics 48*, 105-109 (2000). DOI: 10.1016/S0360-3016(00)00603-9
3. Dawson, L. A., Litzenberg, D. W., Brock, K. K., Sanda, M., Sullivan, M., Sandler, H. M., Balter, J. M. A comparison of ventilatory prostate movement in four treatment positions. *International Journal of Radiation Oncology, Biology, Physics 48*, 319-323 (2000). DOI: 10.1016/S0360-3016(00)00751-3
4. Kitamura, K., Shirato, H., Seppenwoolde, Y., Onimaru, R., Oda, M., Fujita, K., Shimizu, S., Shinohara, N., Harabayashi, T., Miyasaka, K. Three-dimensional intrafractional movement of prostate measured during real-time tumor-tracking radiotherapy in supine and prone treatment positions. *International Journal of Radiation Oncology, Biology, Physics 53*, 1117-1123 (2002). DOI: 10.1016/S0360-3016(02)02882-1
5. Vargas, C., Saito, A. I., Hsi, W. C., Indelicato, D., Falchook, A., Zengm, Q., Oliver, K., Keole, S., Dempsey, J. Cine-magnetic resonance imaging assessment of intrafraction motion for prostate cancer patients supine or prone with and without a rectal balloon. *American Journal of Clinical Oncology 33*, 11-16 (2010). DOI: 10.1097/COC.0b013e31819fdf7c
6. O'Neill, L., Armstrong, J., Buckney, S., Assiri, M., Cannon, M., Holmberg, O. A phase II trial for the optimisation of treatment position in the radiation therapy of prostate cancer. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology 88*, 61-66 (2008). DOI: 10.1016/j.radonc.2008.03.023
7. Weber, D. C., Nouet, P., Rouzaud, M., Miralbell, R. Patient positioning in prostate radiotherapy: is prone better than supine? *International Jour-nal of Radiation Oncology, Biology, Physics 47*, 365-371 (2000). DOI: 10.1016/S0360-3016(99)00458-7
8. Das, I. J., Lanciano, R. M., Movsas, B., Kagawa, K., Barnes, S. J. Efficacy of a belly board device with CT-simulation in reducing small bowel volume within pelvic irradiation fields. *International Journal of Radiation Oncology, Biology, Physics 39*, 67-76 (1997). DOI: 10.1016/S0360-3016(97)00310-6
9. Koelbl, O., Richter, S., Flentje, M. Influence of patient positioning on dose-volume histogram and normal tissue complication probability for small bowel and bladder in patients receiving pelvic irradiation: a prospective study using a 3D planning system and a radiobiological model. *International Journal of Radiation Oncology, Biology, Physics 45*, 1193-1198 (1999). DOI: 10.1016/S0360-3016(99)00345-4
10. Kim, J. Y., Kim, D. Y., Kim, T. H., Park, S. Y., Lee, S. B., Shin, K. H., Pyo, H., Cho, K. H. Intensity-modulated radiotherapy with a belly board for rectal cancer. *International Journal of Colorectal Disease 22*, 373-379 (2007). DOI: 10.1007/s00384-006-0166-x
11. Koelbl, O., Vordermark, D., Flentje, M. The relationship between belly board position and patient anatomy and its influence on dose-volume histogram of small bowel for postoperative radiotherapy of rectal cancer. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology 67*, 345-349 (2003). DOI: 10.1016/S0167-8140(03)00164-6

12. Cheung, P., Sixel, K., Morton, G., Loblaw, D. A., Tirona, R., Pang, G., Choo, R., Szumacher, E., Deboer, G., Pignol, J. P. Individualized planning target volumes for intrafraction motion during hypofractionated intensity-modulated radiotherapy boost for prostate cancer. *International Journal of Radiation Oncology, Biology, Physics 62*, 418-425 (2005). DOI: 10.1016/j.ijrobp.2004.09.051
13. Wilder, R. B., Chittenden, L., Mesa, A. V., Bunyapanasarn, J., Agustin, J., Lizarde, J., Ravera, J., Tokita, K. M. A prospective study of intrafraction prostate motion in the prone vs. supine position. *International Journal of Radiation Oncology, Biology, Physics 77*, 165-170 (2010). DOI: 10.1016/j.ijrobp.2009.04.041
14. Padhani, A. R., Khoo, V. S., Suckling, J., Husband, J. E., Leach, M. O., Dearnaley, D. P. Evaluating the effect of rectal distension and rectal movement on prostate gland position using cine MRI. *International Journal of Radiation Oncology, Biology, Physics 44*, 525-533 (1999). DOI: 10.1016/S0360-3016(99)00040-1
15. Mah, D., Freedman, G., Milestone, B., Hanlon, A., Palacio, E., Richardson, T., Movsas, B., Mitra, R., Horwitz, E., Hanks, G. E. Measurement of intrafractional prostate motion using magnetic resonance imaging. *International Journal of Radiation Oncology, Biology, Physics 54*, 568-575 (2002). DOI:10.1016/S0360-3016(02)03008-0
16. Ghilezan, M. J., Jaffray, D. A., Siewerdsen, J. H., Van Herk, M., Shetty, A., Sharpe, M. B., Zafar Jafri, S., Vicini, F. A., Matter, R. C., Brabbins, D. S., Martinez, A. A. Prostate gland motion assessed with cine-magnetic resonance imaging (cine-MRI). *International Journal of Radiation Oncology, Biology, Physics 62*, 406-417 (2005). DOI: 10.1016/j.ijrobp.2003.10.017
17. Ogino, I., Kaneko, T., Suzuki, R., Matsui, T., Takebayashi, S., Inoue, T., Morita, S. Rectal content and intrafractional prostate gland motion assessed by magnetic resonance imaging. *Journal of Radiation Research 52*, 199-207 (2011). DOI: 10.1269/jrr.10126
18. Beltran, C., Herman, M. G., Davis, B. J. Planning target margin calculations for prostate radiotherapy based on intrafraction and interfraction motion using four localization methods. *International Journal of Radiation Oncology, Biology, Physics 70*, 289-295 (2008). DOI: 10.1016/j.ijrobp.2007.08.040
19. Huang, E., Dong, L., Chandra, A., Kuban, D. A., Rosen, II, Evans, A., Pollack, A. Intrafraction prostate motion during IMRT for prostate cancer. *International Journal of Radiation Oncology, Biology, Physics 53*, 261-268 (2002). DOI: 10.1016/S0360-3016(02)02738-4

Received: December 1, 2012; Revised: January 4, 2013; Accepted: January 18, 2013

ANTICANCER RESEARCH *33*: xxx-xxx (2013)

No: 16372-Z
Please mark the appropriate section for this paper
☐ Experimental
☐ Clinical
☐ Epidemiological

Definitive Fractionated Re-irradiation for Local Recurrence Following Stereotactic Body Radiotherapy for Primary Lung Cancer

TADAMASA YOSHITAKE[1], YOSHIYUKI SHIOYAMA[2], KATSUMASA NAKAMURA[3], TOMONARI SASAKI[3], SAIJI OHGA[3], MAKOTO SHINOTO[3], KOTARO TERASHIMA[3], KAORI ASAI[2], KEIJI MATSUMOTO[3], HIDEKI HIRATA[4] and HIROSHI HONDA[3]

Department of [1]Comprehensive Clinical Oncology, [2]Heavy Particle Therapy and Radiation Oncology, [3]Clinical Radiology, and [4]Health Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Abstract. *Aim: To retrospectively evaluate the efficacy and safety of definitive fractionated re-irradiation for local recurrence following stereotactic body radiotherapy (SBRT) for primary lung cancer. Patients and Methods: Between April 2003 and December 2011, 398 patients with primary lung tumor underwent SBRT at Kyushu University Hospital, and 46 of these patients developed local recurrence after SBRT. Definitive fractionated re-irradiation was performed for 17 out of the 46 patients. The median dose of re-irradiation was 60 Gy/ 30 fractions. Concurrent chemotherapy was given to four patients. Results: The median follow-up duration was 12.6 months. At one year post-re-irradiation, local progression-free survival was 33.8%; progression-free survival, 30.9%; cause-specific survival, 79.3%; and overall survival, 74.7%. No severe adverse events were observed during the follow-up. Conclusion: Definitive fractionated re-irradiation is thought to be safe and an alternative therapy for local recurrence following SBRT, although its efficacy may be not entirely satisfactory.*

Stereotactic body radiotherapy (SBRT) has been used to treat primary and metastatic lung tumors with excellent local control rates. The 3-year local control rate of SBRT for stage I non-small cell lung cancer has been reported to be 78-92% (1-10). However, therapeutic strategies for local recurrence following SBRT have not yet been established. Because most patients who are treated with SBRT are medically inoperable for various reasons prior to SBRT, surgical resection or chemotherapy for local recurrence is not indicated in most cases. Severe adverse events due to re-irradiation to the same site have been a concern, but a number of researchers have reported that palliative and definitive re-irradiation following fractionated radiotherapy for primary and metastatic lung tumors was safe and effective (11-16). The efficacy of fractionated re-irradiation for local recurrence following SBRT, in contrast, is still unknown.

The purpose of the present study was to explore the efficacy and safety of definitive fractionated re-irradiation for local recurrence following SBRT for primary lung cancers.

Correspondence to: Tadamasa Yoshitake, Department of Comprehensive Clinical Oncology, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. Tel: +81 926425695, Fax: +81 926425708, e-mail: yoshitake@radiol.med.kyushu-u.ac.jp

Key Words: Lung cancer, stereotactic body radiotherapy, re-irradiation, fractionation.

Patients and Methods

Patient and tumor characteristics. Between April 2004 and December 2011, 398 patients with primary lung cancer underwent SBRT at Kyushu University Hospital; 46 of these patients (11.6%) subsequently developed local recurrence. Among these 46 patients, definitive fractionated re-irradiation was performed for 17 patients (37.0%) who were medically inoperable or refused surgery. The median age of the 17 patients was 81 years (range=69-88 years). Fifteen patients were male, and two were female. The median size of the recurrent tumors was 41 mm (range=19-77 mm). Three patients had regional lymph node metastases and one had brain metastases. Three out of the 17 patients had regional nodal failure and one had two brain metastases, concurrently. Patient and tumor characteristics are summarized in Table I.

Prior SBRT. The SBRT technique has been described (17). All patients were fixed with a Body Cast System composed of a thermoplastic body cast, a vacuum pillow, arm and leg support, and a carbon plate (Engineering Systems Co., Matsumoto, Japan). Computed tomography (CT) scans were performed at 2-mm intervals on the day of planning and on the first treatment day for verification of the set-up. Treatment planning was performed using the 3D RTP machine (Eclipse: Varian Medical Systems, Palo Alto,

0250-7005/2013 $2.00+.40

Table I. *Patient and tumor characteristics.*

Median age, (years) at re-irradiation (range)	81 (69-88)
Gender (M:F)	15:2
Median radiation dose of prior SBRT, (Gy) (range)	48 (48-60)
Median tumor size at prior SBRT, (mm) (range)	28 (10-51)
Tumor histology, n	
Squamous cell carcinoma	9
Adenocarcinoma	3
Non-small cell carcinoma, NOS	1
Unknown	4
Pattern of failures after SBRT, n	
Local	13
Local + regional	3
Local + distant	1
Method for diagnosis of recurrence after SBRT, n	
Histology	4
Cytology	1
Clinical and radiological findings	12
Performance status at the time of re-irradiation, n	
0	3
1	8
2	5
3	1
Median tumor size of recurrent tumor, (mm)	41 (19-77)
Median interval between SBRT and recurrence, (months)	11.6 (4.8-32.9)
Median interval between treatments, (months)	12.4 (6.3-35.5)

CA, USA). The gross tumor volume (GTV) was identified on relevant lung setting CT images. The internal target volume (ITV) was created individually according to the internal respiratory motion. The planning target volume (PTV) margin was 5 mm in all directions. Seven to eight multi-leaf-collimator (MLC)-shaped non-coplanar static ports of 4 or 6 MV X-rays were selected to reduce the percentage of total lung receiving more than 20 Gy (V20) to below 20% (Figure 1A). The prescribed dose was 48 Gy in four fractions, except for one patient (60 Gy in 10 fractions). When the range of respiratory tumor motion was 1 cm or more, irradiation was performed during breath-holding using a visual feedback-guided breath-holding system (18). No patients received chemotherapy before or after SBRT. No severe adverse events (*i.e.* grade 2 or greater) were observed after SBRT in any patient.

Fractionated re-irradiation. The length of time from the SBRT to the recurrence and to re-irradiation was 4.8-32.9 months (median=11.6 months) and 6.3-35.5 months (median=12.4 months), respectively. Local recurrence was diagnosed by histological or cytological examination in five out of the 17 patients, and by clinical and radiological findings in 12 patients. Definitive fractionated re-irradiation was performed with a dose of 60-70 Gy in 30-35 fractions (median=60 Gy in 30 fractions). The irradiation fields were limited to the recurrent gross tumors without prophylactic lymph node coverage (Figure 1B).

One patient with brain metastases underwent stereotactic radiosurgery prior to the re-irradiation to local recurrence. The lung V20 values of the 17 patients were 3.9%-25.2% (median=9.2%). The cumulative dose (BED10) of the prior SBRT and fractionated re-irradiation ranged from 168 to 189.6 Gy (median=177.6 Gy). Four out of the 17 patients (23.5%) received concurrent chemotherapy (carboplatin plus paclitaxel: n=3; S-1: n=1) with fractionated re-irradiation. One patient (5.9%) received hyperthermia treatment weekly during the radiotherapy. Thirteen patients (76.5%) were treated with radiotherapy alone.

Patient follow-up and evaluation. After the completion of re-irradiation, patients were assessed by examinations including chest X-ray and CT every four weeks for the first six months, every 2-3 months for the next 18 months, and every six months thereafter. Brain magnetic resonance imaging (MRI) and fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) were also performed if needed.

Data analysis. We evaluated the patients' survival rates after re-irradiation, the pattern of failures, and toxicities. Overall survival (OS), cause-specific survival (CSS), progression-free survival (PFS), and local progression-free survival (LPFS) rates were estimated with the Kaplan–Meier method. Toxicities were graded according to the Common Toxicity Criteria for Adverse Effect version 3.0 (CTCAE v3.0) (19).

Results

Survival and patterns of failure. The median follow-up was 12.6 months (range=4.3-31.1 months). Re-recurrence was observed in 11 patients (64.7%). Local re-recurrence was observed in nine patients (52.9%), one out of these with local re-recurrence also had lung metastasis. Regional failure and

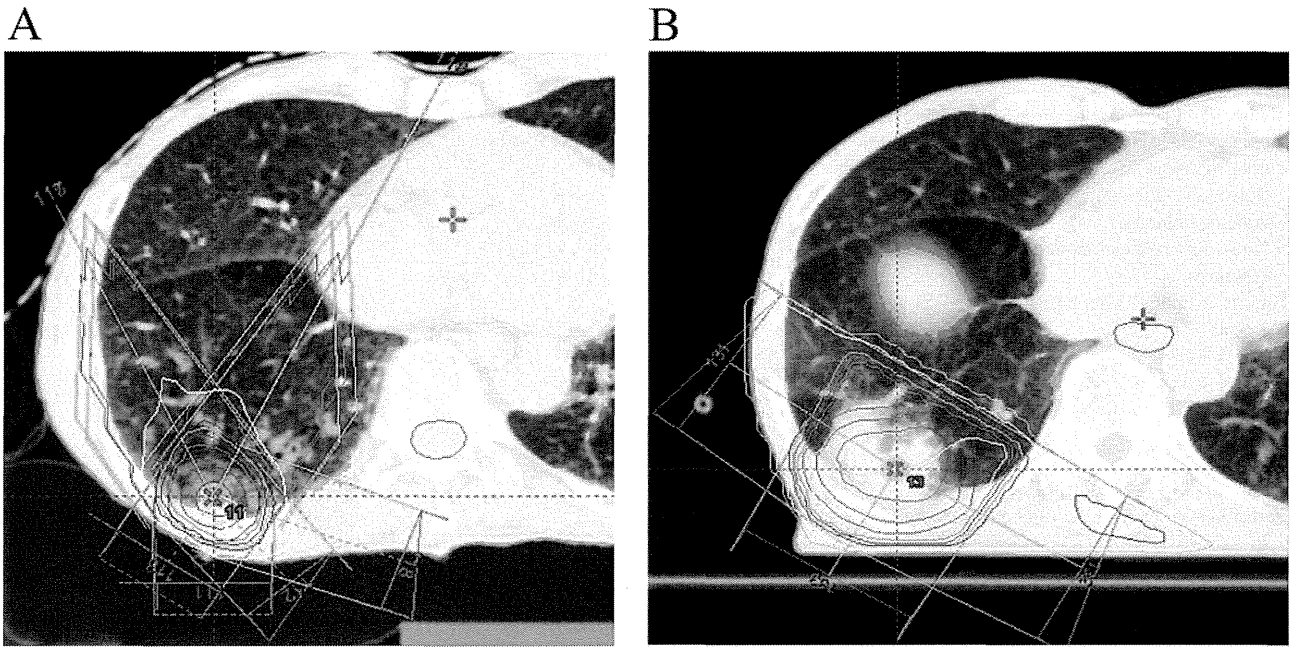


Figure 1. *A computed tomographic (CT) image of a 79-year-old male with cT1aN0M0 squamous cell lung carcinoma of the lower right lobe. A: stereotactic body radiotherapy (SBRT) was performed for primary lung cancer with a dose of 48 Gy in four fractions. B: Re-irradiation with doses of 60 Gy in 30 fractions was performed for local recurrence which was confirmed by CT-guided biopsy 14 months after SBRT. The patient died of another disease one year after re-irradiation, without disease progression.*

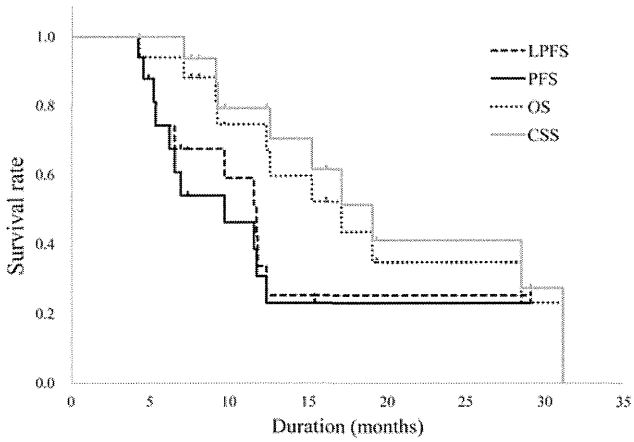
pleural dissemination were each observed in one patient (5.9%). Nine patients (52.9%) died of recurrence, and two (11.8%) died from other diseases.

At one year post-re-irradiation, the following rates were obtained for the 17 patients: LPFS, 33.8%; PFS, 30.9%; CSS, 79.3%; and OS, 74.7% (Figure 2). The median LPFS was 11.7 months; that for PFS was 9.7, for CSS, 19.0, and for OS, 17.0 months.

Adverse effects. One patient had a grade 2 rib fracture. No other adverse events of grade 2 or more were observed in any patient during the follow-up.

Discussion

In this study, the LPFS rate at one year after fractionated re-irradiation was 33.8%, an unacceptably low value. Two reasons may account for the low LPFS; the first is an insufficient dose of fractionated re-irradiation. The biological effective dose of 60 Gy in 30 fractions is smaller than that of 48 Gy in four fractions. In addition, the recurrent tumor might contain potentially radioresistant cells that survived the prior SBRT. The second reason is that the recurrent tumor and the surrounding normal tissue might exhibit hypoxic changes due to microvascular dysfunction as a late effect of the prior radiotherapy (20, 21). In this respect, however, fractionated



Abbreviations: LPFS = local progression-free survival; PFS = progression-free survival; CSS = cause-specific survival; OS = overall survival.

Figure 2. *Survival curves after definitive fractionated re-irradiation. This figure shows Kaplan–Meier curves for the overall survival rate (OS), cause-specific survival rate (CSS), progression-free survival rate (PFS), and local progression-free survival rate (LPFS) of patients after re-irradiation for local recurrence following stereotactic body radiotherapy.*

irradiation takes better advantage of the reoxygenation phenomenon compared to hypofractionated irradiation, which may be reason for long-term local control being observed in

only a few of our patients. Further investigation to determine the optimal dose and fractionation is necessary.

To our knowledge, this is the first report of the feasibility of re-irradiation for local recurrence after SBRT. In previous studies of re-irradiation following fractionated irradiation (12-16), the incidences of grade 2 and 3 radiation pneumonitis were 3%-35% and 0%-21%, and those of esophagitis were 0%-24% and 0%-6%. There were no cases of grade 2 or more esophagitis in this study, unlike the previous studies. We suspect that the reasons for the low incidence of esophagitis are that the irradiation dose to the esophagus was very low in the prior SBRT, and that the field of re-irradiation did not include a prophylactic area. In addition, no grade 2 or more pneumonitis was observed in this study. One of the reasons is probably that none of the patients had severe radiation pneumonitis after the prior SBRT. If the patients had had severe radiation pneumonitis, re-irradiation would not have been performed. This selection bias was one of the limitations of this study.

The single patient who had a rib fracture received medication without surgical treatment and improved. For all of these reasons, fractionated re-irradiation may be a safe treatment option for local recurrence following SBRT. However, if the disease in the patients is initially operable, we need to consider the indications for salvage lung resection prior to re-irradiation. Chen *et al.* reported that salvage surgical resection was feasible after SBRT in patients with initially operable disease (22). In addition, when a patient is epidermal growth factor receptor (EGFR) mutation-positive, re-irradiation can be avoided by using an EGFR-tyrosine kinase inhibitor as a salvage treatment.

In this study, we used a median dose of 48 Gy with four fractions, which is the most frequently used schedule of SBRT in Japan for primary lung cancer (23). This dose is smaller than the doses used in the U.S.A. (24). The efficacy and safety of re-irradiation after higher doses should be evaluated.

In this study, the median LPFS was 11.7 months, and long-term local control was obtained in a few patients. The adverse events are considered acceptable. Therefore, when other treatment methods are difficult to perform, fractionated re-irradiation may be an alternative. To improve the treatment results of re-irradiation for local recurrence after SBRT, dose escalation of fractionated re-irradiation, combinations of chemotherapy, and re-irradiation using an SBRT technique may be effective. To decide the optimal treatment strategy for local recurrence after SBRT, a greater number of patients and prospective randomized trials are necessary.

Conclusion

Definitive fractionated re-irradiation is thought to be safe and an alternative therapy for local recurrence following SBRT, although its efficacy may be not entirely satisfactory.

Acknowledgements

This work was supported in part by JSPS KAKENHI grant numbers 23390302, 23659589.

References

1 Matsuo Y, Shibuya K, Nagata Y, Takayama K, Norihisa Y, Mizowaki T, Narabayashi M, Sakanaka K and Hiraoka M: Prognostic factors in stereotactic body radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys *79*: 1104-1111, 2011.

2 Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, Yamashita T, Niibe Y, Karasawa K, Hayakawa K, Takai Y, Kimura T, Hirokawa Y, Takeda A, Ouchi A, Hareyama M, Kokubo M, Hara R, Itami J and Yamada K: Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: Clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer *101*: 1623-1631, 2004.

3 Hoyer M, Roed H, Hansen A, Ohlhuis L, Petersen J, Nellemann H, Berthelsen A, Grau C, Engelholm S and Vondermaase H: Prospective study on stereotactic radiotherapy of limited-stage non–small-cell lung cancer. Int J Radiat Oncol Biol Phys *66*: S128-S135, 2006.

4 Zimmermann FB, Geinitz H, Schill S, Thamm R, Nieder C, Schratzenstaller U and Molls M: Stereotactic hypofractionated radiotherapy in stage I (T1-2 N0 M0) non-small cell lung cancer (NSCLC). Acta Oncol *45*: 796-801, 2006.

5 Nyman J, Johansson KA and Hulten U: Stereotactic hypofractionated radiotherapy for stage I non-small cell lung cancer – mature results for medically inoperable patients. Lung Cancer *51*: 97-103, 2006.

6 Koto M, Takai Y, Ogawa Y, Matsushita H, Takeda K, Takahashi C, Britton KR, Jingu K, Takai K, Mitsuya M, Nemoto K and Yamada S: A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. Radiother Oncol *85*: 429-434, 2007.

7 Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA and Timmerman R: Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys *75*: 677-682, 2009.

8 Ricardi U, Filippi AR, Guarneri A, Giglioli FR, Ciammella P, Franco P, Mantovani C, Borasio P, Scagliotti GV and Ragona R: Stereotactic body radiation therapy for early stage non-small cell lung cancer: Results of a prospective trial. Lung Cancer *68*: 72-77, 2010.

9 Kopek N, Paludan M, Petersen J, Hansen AT, Grau C and Hoyer M: Co-morbidity index predicts for mortality after stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer. Radiother Oncol *93*: 402-407, 2009.

10 Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, Drugge N, Ekberg L, Friesland S, Johansson KA, Lund JA, Morhed E, Nilsson K, Levin N, Paludan M, Sederholm C, Traberg A, Wittgren L and Lewensohn R: Outcome in a prospective phase II trial of medically inoperable stage I non-small cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol *27*: 3290-3296, 2009.

11 Morris DE: Clinical experience with retreatment for palliation. Semin Radiat Oncol *10*: 210-221, 2000.

12 Jackson MA and Ball DL: Palliative retreatment of locally-recurrent lung cancer after radical radiotherapy. Med J Aust *147*: 391-394, 1987.
13 Okamoto Y, Murakami M, Yoden E, Sasaki R, Okuno Y, Nakajima T and Kuroda Y: Reirradiation for locally recurrent lung cancer previously treated with radiation therapy. Int J Radiat Oncol Biol Phys *52*: 390-396, 2002.
14 Wu KL, Jiang GL, Qian H, Wang LJ, Yang HJ, Fu XL and Zhao S: Three-dimensional conformal radiotherapy for locoregionally recurrent lung carcinoma after external beam irradiation: A prospective phase I-II clinical trial. Int J Radiat Oncol Biol Phys *57*: 1345-1350, 2003.
15 Gressen EL, Werner-Wasik M, Cohn J, Topham A and Curran WJ: Thoracic reirradiation for symptomatic relief after prior radiotherapeutic management for lung cancer. Am J Clin Oncol *23*: 160-163, 2000.
16 Jereczek-Fossa BA, Kowalczyk A, D'Onofrio A, Catalano G, Garibaldi C, Boboc G, Vitolo V, Leonardi MC, Cambria R and Orecchia R: Three-dimensional conformal or stereotactic reirradiation of recurrent, metastatic or new primary tumors. Strahlenther Onkol *184*: 36-40, 2008.
17 Shioyama Y, Nakamura K, Anai S, Sasaki T, Ooga S, Saku M, Urashima Y, Yoshitake T, Toba T, Terashima H and Honda H: Stereotactic radiotherapy for lung and liver tumors using a body cast system: Setup accuracy and preliminary clinical outcome. Radiat Med *23*: 407-413, 2005.
18 Yoshitake T, Shioyama Y, Nakamura K, Ohga S, Nonoshita T, Ohnishi K, Terashima K, Arimura H, Hirata H and Honda H: A clinical evaluation of visual feedback-guided breath-hold reproducibility of tumor location. Phys Med Biol *54*: 7171-7182, 2009.
19 Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN and Rubin P: CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol *13*: 176-181, 2003.
20 Vujaskovic Z, Anscher MS, Feng QF, Rabbani ZN, Amin K, Samulski TS, Dewhirst MW and Haroon ZA: Radiation-induced hypoxia may perpetuate late normal tissue injury. Int J Radiat Oncol Biol Phys *50*: 851-855, 2001.
21 Stone HB, Coleman CN, Anscher MS and McBride WH: Effects of radiation on normal tissue: Consequences and mechanisms. Lancet Oncol *4*: 529-536, 2003.
22 Chen FS, Matsuo Y, Yoshizawa A, Sato T, Sakai H, Bando T, Okubo K, Shibuya K and Date H: Salvage lung resection for non-small cell lung cancer after stereotactic body radiotherapy in initially operable patients. J Thorac Oncol *5*: 1999-2002, 2010.
23 Nagata Y, Hiraoka M, Mizowaki T, Narita Y, Matsuo Y, Norihisa Y, Onishi H and Shirato H: Survey of stereotactic body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiotherapy Group. Int J Radiat Oncol Biol Phys *75*: 343-347, 2009.
24 Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E and Choy H: Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA *303*: 1070-1076, 2010.

Received July 20, 2013
Revised October 24, 2013
Accepted October 28, 2013

未来の放射線治療の方向性

塩山善之*

索引用語：放射線治療，高度化，多様化，センター化，個別化

1 はじめに

近年の放射線治療技術の進歩は著しく，定位放射線治療，強度変調放射線治療といった高精度エックス線照射技術は各領域の固形癌に対する放射線治療において治療効果の向上および副作用の低減に寄与しているのは間違いない．さらに，陽子線，炭素イオン線を用いた粒子線治療も研究段階から本格的な臨床応用，普及といった段階に入り，その特徴的な深部線量分布(飛程を持ち停止する直前で線量のピークを形成)を利用することにより線量集中性がさらに改善され，副作用のさらなる軽減および二次発癌リスクの低減が可能と期待されている．これらの放射線治療技術の進歩が肝胆膵領域の癌治療にも活かされていることは各項に述べられている通りである．高精度エックス線治療，陽子線治療，炭素イオン線治療は，それぞれ，従来型の放射線治療に比較して非常に有効な治療法であることは間違いないが，一方で，このように多様化した放射線治療技術をどのように使い分ければ良いのかという点では臨床現場にある意味で混乱を招いているのも事実である．また，内科領域では分子標的薬剤や免疫療法，外科領域ではロボット手術に代表される低侵襲外科治療，さらには，再生医療が癌治療の分野も注目されている時代であり，癌治療法はこれまでになく多様化の様相を呈している．

本稿では「未来の放射線治療の方向性」という非常に大きなテーマを頂き，どのように話をまとめれば良いのか苦慮するところではあるが，私が考えるあるべき将来の方向性について述べてみたい．

2 高精度エックス線治療と粒子線治療のベストミックスを探る時代へ

100年以上に及ぶ放射線治療の長い歴史を考えても，250kVエックス線からガンマ線，そして現在の主流である高エネルギーエックス線と癌治療に用いられる放射線は時代とともに癌治療により適したものへ変化してきた．この事実を考えた場合，将来的には陽子線や炭素イオン線といった粒子線治療が放射

Yoshiyuki SHIOYAMA : Future direction of radiotherapy
*九州国際重粒子線がん治療センター［〒841-0071 佐賀県鳥栖市原古賀町415］

線治療の主役を担う時代が訪れてもおかしくないとも考えることができる．しかし，癌の病態はさまざまであり，腫瘍の性質や拡がりなどにより最適な治療法は異なり，ただ単に病巣への線量集中のみが求められるわけではなくエックス線やガンマ線治療の必要性は必ず残ると思われる．例をあげれば，咽頭癌などの頭頸部扁平上皮癌の放射線治療においては，頸部・鎖骨上領域といった広い範囲の系統的なリンパ節領域照射を合わせて行う必要があるため，エックス線を用いた強度変調放射線治療の方がむしろ適しているし，全骨盤照射＋小線源療法で根治可能な子宮頸癌をあえて粒子線で治療する必要もないであろう．その他にも全脳照射や乳癌術後照射，多くの緩和照射などさまざまな状況でエックス線治療はなくてはならない存在である．また，転移性脳腫瘍に対する定位照射もこれまで同様エックス線やガンマ線を用いた治療がその主役を担い続けるであろう．

一方，頭頸部の非扁平上皮癌，肺縦隔腫瘍，消化管原発を除く腹部骨盤部腫瘍などの多くの限局性の癌では，粒子線治療の線量分布の良さを活かしたさらなる低リスク放射線治療を目指すべきと思われる．もちろん，肺や肝臓の小さな腫瘍であれば定位照射で良好な成績が得られているが，粒子線治療を用いることにより副作用のさらなる低減に加え，これまで制御が困難であった比較的大きな腫瘍に対する局所制御も期待できる[1]．特に，肝胆膵の領域に目を向けると，肝細胞癌のようにベースに慢性肝機能障害を有する患者では，周囲正常肝の線量および照射容積を最小限に留められる粒子線治療は肝機能温存の点でメリットは大きく[2~4]，肝内再発例に対する複数回治療にも有利となる[5]．また，胆管癌や膵臓癌の治療においても比較的放射線感受性の高い正常肝，腎臓，腸管への線量を少なくできる点でエックス線治療に比較し明らかに有利である．また，膵癌や胆管癌治療においては，抗癌剤併用時の副作用低減にも役立つ．特に，炭素イオン線では生物学的効果が高く膵癌や胆管癌といった放射線低感受性腫瘍に対するさらなる効果も期待される[6]．

高精度エックス線治療 vs. 陽子線治療，陽子線治療 vs. 炭素イオン線治療といった構図で議論されることも多い昨今ではあるが，いずれも今後の放射線治療の発展には必要不可欠なものであり，より効果的かつ低リスクの放射線治療を確立するために，これらを如何に使い分け，また，いかに組み合わせるかを議論し検証していくことが重要な点である．粒子線治療は未来の放射線治療の可能性を大きく広げる治療法であることは間違いなく，その有効性を確認しながら，癌医療の中に着実に定着させていかなければならない．そのためには，粒子線治療施設の適正な配置と有効利用，臨床試験をベースとした質の高いエビデンスの蓄積，装置の小型化・低コスト化と普及がバランス良く行われていくことが極めて重要と思われる．

3 「均てん化」と「センター化」のベストバランスを探る時代へ

放射線治療は2004年から開始された第3次対癌10カ年総合戦略の重要な柱であり「癌医療水準の均てん化」のもと，放射線治療機器の整備や放射線治療医や医学物理士などの専門医療スタッフの育成が図られてきた．地域格差を是正し放射線治療の質を確保するという観点から一定の成果を上げてきたが，放射線治療機器の分散や増加する放射線治療のニーズに人材育成が追いついていないのが現状である．さらには，高精度X線治療，陽子

線治療，炭素イオン線治療といった放射線治療の高度化・多様化も加わり「均てん化」のみでは対応できないことも明らかとなってきている．事実，2012年6月に策定された厚生労働省の新たながん対策基本計画では，「一部の疾患や強度変調放射線治療などの治療技術の地域での集約化」という文言が盛り込まれている[7]．日本においても今後，強度変調放射線治療，陽子線治療，炭素イオン線治療といった高度な放射線治療技術に関しては「センター化」の方向性で整備が進められていく必要があろう．特に，粒子線治療においては「センター化」という観点での適正配置と有効活用が極めて重要な領域であり，そのためには，本当の意味での機能的な医療連携ネットワークの構築が必要である．また，センター化された数少ない施設を有効に活用するには，紹介側の医療機関との役割分担も大事であり，他の施設に入院中の患者が治療を受ける際でも保険制度上問題とならないような制度上の環境整備が同時に行われなければならない．粒子線治療分野は放射線治療におけるセンター化の良いモデルケースにならなければならない．

4 解剖学的画像ベースから機能・分子画像ベースの放射線治療の時代へ

従来の放射線治療計画は3次元治療計画が主体であったが，近年では腫瘍の呼吸性移動を考慮した4次元治療計画の時代となり，照射技術的にも呼吸同期照射や動体追尾照射や迎撃照射が可能となってきている．しかし，これまでの治療計画は主に形態画像(主にCT)を中心に行われ，腫瘍内の機能や組織環境，周囲正常臓器の内部の機能はあまり考慮されていなかった．一方，近年の分子・機能イメージング分野の進歩は著しく，一般的なものとしては，糖代謝を画像化したF-18 FDG-PETが癌の病期診断や予後予測，再発診断などに広く用いられており，放射線治療計画においても正確な標的体積の設定という点での有用性も高い．その他にも，アミノ酸代謝をみるC-11メチオニン，拡散代謝をみるF-18 FLT，低酸素細胞をみるF-18 MISO，Cu-62 ATSMなどの分子腫瘍イメージングの臨床研究・臨床応用も盛んに行われている．強度変調放射線治療や粒子線治療(特にペンシルビームによるスキャンニング照射)は，腫瘍内部を場所によって線量強度を変えて照射することができ，上記のような分子イメージングと治療計画上融合することにより，腫瘍内のviabilityの高い領域や低酸素領域(放射線低感受性)に線量高度を高めることも可能となり，さらなる局所制御・予後向上に役立つものと思われる[8]．

また，周囲正常臓器の機能画像を治療計画に用いて線量分布を最適化することによって，腫瘍発生臓器やその周囲正常臓器の機能低下を最小限に留めようとする試みも行われている．例をあげれば，肺癌に対する強度変調放射線治療の治療計画に肺血流シンチや4次元換気CT画像を用いて高い機能が残っている領域の照射線量・容積を減らし治療後の機能低下を最小限に留めるというアプローチである[9,10]．肝胆膵領域の治療においては，術後の肝予備能の予測における肝受容体シンチ(アシアロシンチ)の有用性が示唆されており，このような機能画像を用いることで，肝胆膵領域の放射線治療の最適化が今後可能となるかもしれない[11,12]．

いずれにしても，未来の放射線治療では分子腫瘍イメージングや正常臓器の機能イメージングを放射線治療の最適化に応用し，さらなる局所効果の向上と低リスク化を図るとい

う方向性が必要であろう．

5 内科・外科治療とのさらなる協調の時代へ

前述のように放射線治療技術の進歩により病巣への線量集中性は著しく改善している．しかし，肝胆膵領域の癌治療においては線量集中性の改善による局所効果の改善と副作用低減だけでは予後向上には限界があるのは自明である．肝細胞癌における陽子線治療，炭素イオン線治療の局所制御率90％前後と極めて高いが，生存率の向上には，術後再発予防と同様に肝内再発をいかに予防するかという点でのアプローチが今後必要と考えられる．切除後の再発予防治療として分子標的治療薬，非環式レチノイド，インターフェロン，免疫療法(癌ワクチン療法，免疫細胞療法)，B型肝炎についてはラミブジンなどの有用性が示唆されているが，放射線治療後の再発予防治療としては効果と安全性の両面でどのような治療法が最も適しているかという意味でも今後検討が必要であろう．また，胆道癌，膵臓癌の根治治療においては潜在的な転移巣制御の観点から抗癌剤との併用は必須であり現在，ジェムザールやTS-1などとの併用療法が行われている．まずは，高精度放射線治療や粒子線治療とこれら抗癌剤の併用療法に関するエビデンスの蓄積が必要であるが，将来的には有効性が期待されているエルロチニブなどの分子標的薬剤や免疫療法との併用療法の可能性についても検討されるべきだろう．

腹部・骨盤部領域の腫瘍に高線量を投与する際に最も障害になるもののひとつは腸管である．現在，粒子線(特に炭素イオン線)領域では，腫瘍と腸管が非常に近接している場合に，外科と連携し腫瘍と腸管の間に距離を保つためのスペーサー留置を行ったうえで照射治療を行うことがあり，より生体親和性の高いスペーサー材料の研究開発も進んでいる．術前・術後照射，再発時の救済治療(救済手術，救済放射線治療)とは別の外科・放射線科との連携オプションとして将来的な発展が望まれる[13]．

6 放射線生物学をベースとした治療の個別化の時代へ

線量集中性の向上により従来に比べて格段に副作用は軽くなってきているのは事実であるが，重篤な有害反応の出現は皆無でない．もちろん，線量分布や投与線量の問題が原因で起こる有害反応もあるが，想定外の重篤な副作用の多くは患者側の因子(体質)に起因している場合が多い．近年のゲノムサイエンスの進歩により遺伝子多型解析が進んでおり，遺伝子多型が薬剤への応答性，放射線への応答性に深く関与していることが判ってきている．今後，正常組織の放射線感受性に関わる遺伝子多型が網羅的に解析されることにより，有害反応が起きやすい症例，起きにくい症例が治療前に推定できるようになり，放射線治療に適した症例の選択法，リスクに応じた放射線治療の個別化が確立されることが望まれる[14]．また，放射線治療後の晩期有害事象の治療法としての再生医療の応用についても本格的な基礎研究，臨床研究が勢力的に行われていくことも期待したい．

7 最後に

未来の放射線治療の方向性について概説した．多分に個人的な意見が含まれており，内容によっては意見の異なる読者の方もおられるであろう．放射線治療に限らず癌医療を取り巻く環境は大きく変化し非常に多様化している．しかし，求められている癌治療は，「よ

り効果的で，より体にやさしい治療」であることは間違いなく，その点で，高精度放射線治療や粒子線治療への期待は非常に大きいと思われる．分子イメージング，生物学の進歩を取り入れながら，また，内科，外科との協力のもとさらに発展することが望まれる．

文　献

1) Sugahara S, Oshiro Y, Nakayama H et al : Proton beam therapy for large hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 76 : 460–466, 2010
2) Kato H, Tsujii H, Miyamoto T et al : Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis. Int J Radiat Oncol Biol Phys 59 : 1468–1476, 2004
3) Imada H, Kato H, Yasuda S et al : Comparison of efficacy and toxicity of short-course carbon ion radiotherapy for hepatocellular carcinoma depending on their proximity to the porta hepatis. Radiother Oncol 96 : 231–235, 2010
4) Hata M, Tokuuye K, Sugahara S et al : Proton beam therapy for hepatocellular carcinoma patients with severe cirrhosis. Strahlenther Onkol 182 : 713–720, 2006
5) Hashimoto T, Tokuuye K, Fukumitsu N et al : Repeated proton beam therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 65 : 196–202, 2006
6) Shinoto M, Yamada S, Yasuda S et al : Phase 1 trial of preoperative, short-course carbon-ion radiotherapy for patients with resectable pancreatic cancer. Cancer 119 : 45–51, 2013
7) 厚生労働省ホームページ http://www.mhlw.go.jp/bunya/kenkou/gan_keikaku.html
8) Bentzen SM, Gregoire V : Molecular imaging-based dose painting: a novel paradigm for radiation therapy prescription. Semin Radiat Oncol 21 : 101–110, 2011
9) Shioyama Y, Jang SY, Liu HH et al : Preserving functional lung using perfusion imaging and intensity-modulated radiation therapy for advanced-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 68 : 1349–1358, 2007
10) Yaremko BP, Guerrero TM, Noyola-Martinez J et al : Reduction of normal lung irradiation in locally advanced non-small-cell lung cancer payients, using ventilation images for functional avoidance. Int J Radiat Oncol Biol Phys 68 : 562–571, 2007
11) Fukui A, Murase K, Tsuda T et al : Assessment of liver function in chronic liver diseases and regional function of irradiated liver by means of 99mTc-galactosyl-human serum albumin liver scintigraphy and quantitative spectral analysis. Ann Nucl Med 14 : 467–476, 2000
12) Nanashima A, Abo T, Kudo T et al : Usefulness of examining hepatic functional volume using technetium-99m galactosyl serum albumin scintigraphy in hepatocellular carcinoma. Nucl Med Commun 34 : 478–488, 2013
13) Komatsu S, Hori Y, Fukumoto T et al : Surgical spacer placement and proton radiotherapy for unresectable hepatocellular carcinoma. World J Gastroenterol 16 : 1800–1803, 2010
14) Alsner J, Andreassen CN, Overgaard J : Genetic markers for prediction of normal tissue toxicity after radiotherapy. Semin Radiat Oncol 18 : 126–135, 2008

*　　*　　*

Radiotherapy and Oncology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Monotherapeutic high-dose-rate brachytherapy for prostate cancer: A dose reduction trial

Yasuo Yoshioka [a,*], Koji Konishi [b], Osamu Suzuki [a], Yasutomo Nakai [c], Fumiaki Isohashi [a], Yuji Seo [a], Yuki Otani [a], Masahiko Koizumi [a], Ken Yoshida [d], Hideya Yamazaki [e], Norio Nonomura [c], Kazuhiko Ogawa [a]

[a] Department of Radiation Oncology, Osaka University Graduate School of Medicine; [b] Department of Radiation Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases; [c] Department of Urology, Osaka University Graduate School of Medicine; [d] Department of Radiology, Osaka Medical College; and [e] Department of Radiology, Kyoto Prefectural University of Medicine, Japan

ARTICLE INFO

Article history:
Received 3 December 2012
Received in revised form 16 July 2013
Accepted 14 October 2013
Available online xxxx

Keywords:
Prostate cancer
Radiotherapy
High-dose-rate (HDR) brachytherapy
Monotherapy
Hypofractionation

ABSTRACT

Purpose: To report preliminary results of our second regimen with 45.5 Gy/7 fractions aiming to reduce toxicity, compared with our first regimen with 54 Gy/9 fractions, using high-dose-rate (HDR) brachytherapy as monotherapy for prostate cancer.

Materials and methods: From 2005 through 2010, 63 patients with localized prostate cancer were treated with HDR brachytherapy alone in 45.5 Gy/7 fractions for 4 days. Thirty-four patients were considered as intermediate-risk and 29 as high-risk. Thirty-seven patients also received neoadjuvant and/or adjuvant hormonal therapy. Biologically effective dose assuming $\alpha/\beta = 1.5$ Gy ($BED_{1.5}$) was reduced from 270 Gy to 243 Gy, and $BED_{3.0}$ from 162 Gy to 144 Gy, compared to previous 54 Gy/9 fractions for 5 days.

Results: Median follow-up time was 42 months (range 13–72). Grade 2 acute toxicities occurred in six (9.5%), late toxicities in five (7.9%) patients, and Grade 3 or higher in none. Grade 2 late gastrointestinal toxicity rate was 1.6%, compared with 7.1% for the 54 Gy regimen. Three-year PSA failure-free rates for intermediate- and high-risk patients were 96% and 90%, which were comparable to 93% and 85% for the 54 Gy regimen.

Conclusions: Compared to the 54 Gy/9 fractions regimen, dose-reduced regimen of 45.5 Gy/7 fractions using HDR brachytherapy as monotherapy preliminarily showed an equivalent or lower incidence rate for acute and late toxicities without compromising the excellent PSA failure-free rate. Further studies with more patients and longer follow-up are warranted.

© 2013 Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology xxx (2013) xxx–xxx

There are multiple treatment options for clinically localized prostate cancer, including radical prostatectomy, external beam radiotherapy (EBRT) [1,2], low-dose-rate (LDR) brachytherapy as monotherapy [3,4], and a combination of EBRT plus LDR brachytherapy [5,6] or high-dose-rate (HDR) brachytherapy [7,8]. Brachytherapy as LDR permanent seed implant or HDR afterloading can deliver a high localized radiation dose to the tumor. LDR brachytherapy has been examined and evaluated the most and become a standard treatment option; while recently HDR brachytherapy is gaining momentum as an alternative to LDR. Several features of HDR brachytherapy, including uniformly accurate, precise, and reproducible dosimetry resulting from optimization capabilities, radiobiologic and radioprotection advantages and reduced costs, make HDR appealing for the treatment of prostate cancer. These merits eliminate the dosimetric uncertainties of LDR related to postimplant volume changes due to needle trauma and subsequent edema during the several months of overall treatment time. HDR significantly improves the radiation dose distribution because it can modulate and accurately control both the spatial source position and dwell time during treatment.

Researchers first used HDR brachytherapy for boosting EBRT in the 1980s. However, to maximize the above-mentioned physical and biological advantages of HDR, HDR monotherapy seems to be the most efficacious with the shortest treatment period. Having used regimens of 48 Gy/8 fractions or 54 Gy/9 fractions since 1995, we were the first to report on the use of HDR brachytherapy without EBRT [9]. We subsequently reported promising preliminary and interim outcomes [10–12]. In 2005, however, we terminated those regimens after using them for 10 years and moved onto a new regimen of 45.5 Gy/7 fractions in order to reduce the radiation dose. We made a hypothesis that we could reduce toxicity by a moderate dose de-escalation, while keeping the excellent outcomes. The aim of the current study is to report the preliminary results of trial with this de-escalated dose regimen, discuss its rationale in terms of biologically effective dose (BED), as well as review the literature on HDR brachytherapy as monotherapy.

* Corresponding author. Address: Department of Radiation Oncology, Osaka University Graduate School of Medicine, 2-2 (D10) Yamadaoka, Suita, Osaka 565-0871, Japan.
E-mail address: yoshioka@radonc.med.osaka-u.ac.jp (Y. Yoshioka).

0167-8140/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2013.10.015

Please cite this article in press as: Yoshioka Y et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: A dose reduction trial. Radiother Oncol (2013), http://dx.doi.org/10.1016/j.radonc.2013.10.015

Patients and methods

Patient selection and characteristics

Between 2005 and 2010, a total of 63 consecutive patients were treated with HDR brachytherapy as monotherapy for clinically localized prostate cancer in the scheme of prospective trial. The eligibility criteria were (1) clinical TNM Stage T1c–T3b, or T4 with only bladder neck invasion and without nodal or other distant metastases as established by clinical, biochemical, and imaging studies, including magnetic resonance imaging, computed tomography (CT), and bone scans; (2) candidacy for epidural anesthesia; (3) data on pretreatment transrectal ultrasound (TRUS) and serum prostate-specific antigen (PSA) levels accessible; and (4) informed consent. Patients were eligible for treatment independent of gland size provided a sufficiently broad pelvic inlet and freedom from lower urinary tract symptoms. Patients were considered ineligible when they had previous pelvic radiotherapy for another malignancy, previous surgery or transurethral resection of the prostate, or prostate cancer recurrence. This study was approved ethically by the institutional review board.

The median age at diagnosis was 69 years (range, 50–82). All patients had biopsy-proven adenocarcinoma of the prostate. According to the 2002 International Union Against Cancer TNM staging system, 15 patients had T1, 32 had T2, 14 had T3 and two had Stage T4. Pretreatment PSA level was 3.9–378.5 ng/ml (median 11.5), including 26 patients with a PSA level <10.0 ng/ml, 22 with 10.0–19.9 ng/ml, and 15 with a PSA level ⩾20.0 ng/ml. Eleven patients had a Gleason score of ⩽6, 34 a score of 7, and 18 a score of 8 or 9. We defined low-risk patients as those with a pretreatment PSA level of <10.0 ng/ml, Gleason score of ⩽6, and Stage T1c–T2a; intermediate-risk patients as those with PSA ⩾10 but <20 ng/ml, Gleason score 7, or Stage T2b–T2c; and high-risk patients as those with PSA ⩾20.0 ng/ml, Gleason score ⩾8, or Stage T3–T4. Thirty-four patients were classified as intermediate risk, and the other 29 as high risk.

In our protocol, patients with only one intermediate-risk feature were not given hormone therapy. The other intermediate-risk and all high-risk patients received 6–12 months of neoadjuvant hormone therapy but no adjuvant. However, if the patients refused hormone therapy, it was skipped. If high-risk patients preferred long-term hormone therapy after being informed of survival benefit of it in case of EBRT, adjuvant hormone therapy was allowed up to 3 years as a total duration. A total of 37 patients (59%) received hormone therapy, consisting of androgen deprivation. Hormone therapy was administered neoadjuvantly to these patients and continued adjuvantly for 14 (38%). The median duration of neoadjuvant and adjuvant hormone therapy was 7 and 18 months. Hormone therapy was administered more frequently to high-risk patients (25 of 29 patients, 86%) than to intermediate-risk patients (12 of 34 patients, 35%). Patient and tumor characteristics are shown in Table 1.

Monotherapeutic HDR brachytherapy technique

The implant technique has been previously described in detail by us [9]. In brief, it involved continuous epidural anesthesia, real-time TRUS guidance, the use of metallic applicators and applicator stoppers (Trocar Point Needles and Needle Stoppers; Nucletron, Veenendaal, The Netherlands), and an original template and its cover plate (Taisei Medical, Osaka, Japan).

The clinical target volume (CTV) included the whole prostate gland with a 5 mm margin except for the posterior (rectal) margin, which varied from 2 to 5 mm depending on the distance to the rectal wall. If extracapsular and/or seminal vesicle invasion was observed or strongly suspected, that area was included in the CTV and applicators were placed there. The planning target volume (PTV) was equal to the CTV, except for in the cranial direction, where it was 1 cm larger and included the bladder base. The top 2 cm of the applicators were placed within the bladder pouch, such that the PTV included a 1-cm margin in the cranial direction from the CTV. This margin was established, not only to avoid the cold area at the base of the prostate, but also to compensate for possible needle displacement in the caudal direction.

CT-based treatment planning was performed with the aid of PLATO (Nucletron) using geometric optimization (volume method) and manual modification. The prescription dose point was positioned 5 mm distant from one source in the central plane. The following dose constraints were applied: the dose to the whole urethra should be 100–150% of the prescription dose, preferably <125%, and the dose to the whole rectal mucosa should be <100% of the prescription dose, preferably <80%. The PTV coverage requirements were D90 >100%, D95 >100% and V100 >97%. The dose-volume constraint for the rectum was D5 cc <55%, which was drawn from our previous analysis, where D5 cc <27 Gy was a significant cut-off value for late rectal toxicity [13]. The BED of 27 Gy in 9 fractions corresponded to 55% of the prescription dose in this study.

The epidurally anesthetized patients remained in bed for 4 days from Monday to Thursday and underwent irradiation twice daily with an interval of ⩾6 h. The treatment consisted of 7 fractions of 6.5 Gy each (total 45.5 Gy). Its BED and biologically equivalent dose in 2-Gy fractions (EQD_{2Gy}) are discussed in detail in the Discussion section together with our rationale. Prophylactic antibiotics were administered twice daily from the day of implant to Day 5. Air-pumping devices were attached to the patients' lower legs to prevent deep vein thrombosis from the day of implant to Day 4. One hour before administration of each irradiation fraction, a urinary balloon catheter was clipped in place to keep the urine within the bladder pouch so that the opposite side of the bladder wall and the bowels were kept away from the irradiation field. To ensure the correct needle position, radiation oncologists confirmed that no

Table 1
Patient characteristics.

Characteristic	Value
Number of patients	63
Age	
Median	69
Range	50–82
T classification	
T1	15 (24%)
T2	32 (51%)
T3	14 (22%)
T4	2 (3%)
Gleason score	
6	11 (17%)
7	34 (54%)
8/9	18 (29%)
Pretreatment PSA (ng/ml)	
<10.0	26 (41%)
10.0–19.9	22 (35%)
⩾20.0	15 (24%)
Median	11.5
Range	3.9–378.5
Risk group	
Intermediate	34 (54%)
High	29 (46%)
Hormone therapy	
Yes	37 (59%)
No	26 (41%)
Follow-up (mo)	
Median	42
Range	13–72

PSA = prostate-specific antigen.

Please cite this article in press as: Yoshioka Y et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: A dose reduction trial. Radiother Oncol (2013), http://dx.doi.org/10.1016/j.radonc.2013.10.015

abnormal space was present between the perineum and template, no unexpected edema was present in the perineum, and none of the needle ends protruded unexpectedly compared with the others before each irradiation fraction. However, routine repositioning of the inserted needles before each session (for example, radiography before each session) was not performed. Instead, as mentioned above, we used a 1-cm PTV margin in the cranial direction so that it covered the CTV adequately even when the needles had moved ⩽1 cm in the caudal direction. We had collected data on needle displacement in the very early period of our previous study [12] and had found that unexpected changes in needle position were distributed between 0 and 1 cm in the caudal direction in most sessions for most patients. However, the data were not meant for publication. We are now testing a new method to adjust the source dwell positions to an original position by moving them to the tip-side space in the displaced needles, referring to the gravity of implanted metal markers for an indicator, using CT before each irradiation fraction; but we had not yet done so in the current study.

Follow-up and toxicity assessment

A radiation oncologist and urologist conducted the follow-up evaluations at least every 3 months, including PSA determinations and queries about urinary and bowel symptoms. PSA failure was defined as the nadir plus 2 ng/ml in accordance with the Radiation Therapy Oncology Group/American Society for Therapeutic Radiology and Oncology Phoenix Consensus Conference recommendations. Acute and late toxicity was scored according to the Common Terminology Criteria for Adverse Events, version 3.0. Acute toxicity was defined as symptoms observed during or after treatment that had completely resolved by 6 months after treatment. Treatment-related toxicity that persisted >6 months after treatment completion was considered late toxicity. Primary endpoints of this study were acute and late toxicities of Grade 2 or more. Secondary endpoint was PSA failure-free rate. The expected outcomes were as follows; Grade 3 toxicity being minimized to be near zero, and Grade 2 toxicity reduced, while PSA failure-free rate maintained, in comparison to our previous report [12]. Erectile function was not evaluated in this study due to the hormone therapy in the majority of patients. The median follow-up time was 42 months (range 13–72).

Statistical analysis

Fisher's exact test was used to compare percentages for the two groups, while the unpaired t test was used to compare the average values. PSA failure-free rates were calculated with the Kaplan and Meier method. Values of $p < 0.05$ were considered significant. Statistical analysis was performed with IBM SPSS Statistics 20 software (IBM, Armonk, NY, USA).

Results

Clinical outcome

No patients were lost to follow-up. Of the 63 patients, five developed PSA failure, three without clinical events and two showing evidence of bone metastases. The three-year actuarial overall survival and metastasis-free survival rates were 100% and 98%. The three-year actuarial PSA failure-free rates for intermediate-risk and high-risk patients were 96% and 90% (Figs. 1 and 2). Hormone therapy had no impact on PSA failure-free rate ($p = 0.985$).

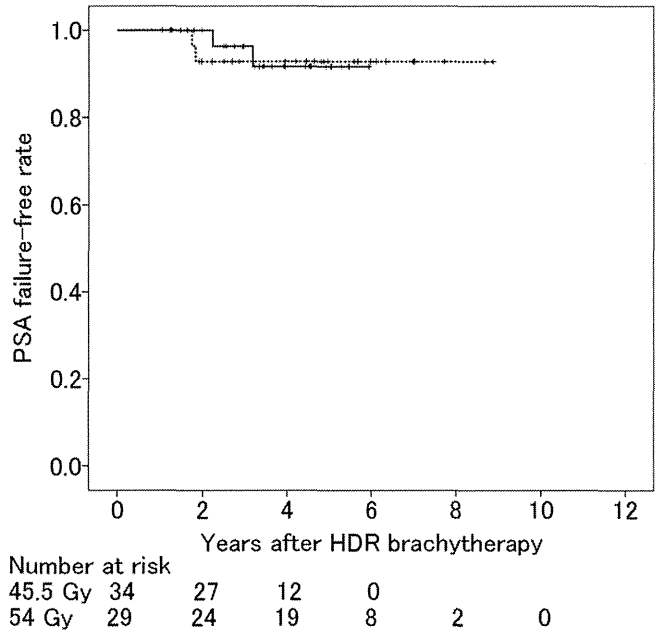


Fig. 1. PSA failure-free rates for intermediate-risk patients (solid line = 45.5 Gy/7 fractions; dashed line = 54 Gy/9 fractions).

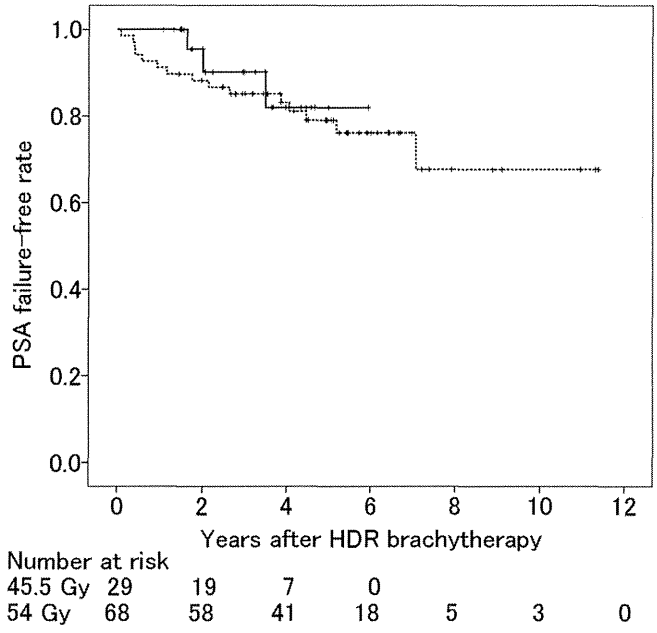


Fig. 2. PSA failure-free rates for high-risk patients (solid line = 45.5 Gy/7 fractions; dashed line = 54 Gy/9 fractions).

Acute toxicity

While no Grade 3 or higher acute toxicity was detected, 6 patients (10%) experienced Grade 2 acute toxicity (all with urinary frequency/urgency). For comparison, Table 2 shows details of acute toxicity for both this study (45.5 Gy/7 fractions group) and our previous study (54 Gy/9 fractions group) [12]. The average of D10 of the urethra was significantly higher in the patients with Grade 2 acute toxicity (70.6 ± 8.7 Gy, average ± standard deviation) than in the other patients with Grade 0/1 (62.5 ± 4.7 Gy) ($p = 0.009$). The other dosimetric parameters (D_{max}, D5, D30, D90, V100, V110, V120, V130, V140, V150 of the urethra, or D1 cc, D2 cc,

Please cite this article in press as: Yoshioka Y et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: A dose reduction trial. Radiother Oncol (2013), http://dx.doi.org/10.1016/j.radonc.2013.10.015

Table 2
Acute and late toxicity of grade 2 or more in two groups of 45.5 Gy/7 fractions and 54 Gy/9 fractions.

Toxicity	45.5 Gy/7 fractions				54 Gy/9 fractions			
	Total	Toxicity grade			Total	Toxicity grade		
		2	3	4		2	3	4
Acute toxicity								
Genitourinary toxicity								
Hematuria	63	0	0	0	112	3 (3%)	1 (1%)	0
Urethral pain	63	0	0	0	112	0	1 (1%)	0
Urinary frequency/urgency	63	6 (10%)	0	0	112	13 (12%)	3 (3%)	0
Urinary retention	63	0	0	0	112	3 (3%)	1 (1%)	0
Gastrointestinal toxicity								
Anal pain	63	0	0	0	112	1 (1%)	0	0
Constipation	63	0	0	0	112	1 (1%)	0	0
Late toxicity								
Genitourinary toxicity								
Hematuria	63	1 (2%)	0	0	112	1 (1%)	0	0
Urethral stricture/stenosis	63	0	0	0	112	1 (1%)	1 (1%)	0
Urinary frequency/urgency	63	2 (3%)	0	0	112	2 (2%)	0	0
Urinary pain	63	1 (2%)	0	0	112	2 (2%)	0	0
Urinary retention	63	0	0	0	112	1 (1%)	0	0
Gastrointestinal toxicity								
Rectal bleeding	63	1 (2%)	0	0	112	6 (5%)	0	0
Rectourethral fistula	63	0	0	0	112	0	1 (1%)	0
Sigmoid colon perforation	63	0	0	0	112	0	1 (1%)	0

Grade: the Common Terminology Criteria for Adverse Events, version 3.0.

D5 cc, D10 cc of the bladder) did not correlate significantly to Grade 2 acute toxicity.

Late toxicity

No Grade 3 or higher late toxicity was detected, but four patients (6%) experienced Grade 2 late genitourinary toxicity (two with urinary frequency/urgency, and one each with hematuria and urinary pain), and one patient (2%) suffered Grade 2 late rectal bleeding. For comparison, Table 2 shows details of late toxicity for both this study (45.5 Gy/7 fractions group) and our previous study (54 Gy/9 fractions group) [12]. The above-mentioned dosimetric parameters of the urethra or the bladder in the patients with Grade 2 late genitourinary toxicity were not significantly different from the other patients with Grade 0/1. The only patient with Grade 2 late rectal bleeding did not have any peculiar value in terms of D1 cc, D2 cc, D5 cc, or D10 cc of the rectum.

Discussion

Historically, HDR brachytherapy was introduced to boost EBRT [7,8]. However, this combination typically adds 4–5 weeks to the time needed for completion of EBRT in addition to hospitalization for HDR brachytherapy. In contrast, if a satisfactory dose distribution could be achieved with HDR brachytherapy alone without EBRT, it would definitely be the most efficient method to achieve a high degree of conformity and dose escalation. For this purpose, we initiated HDR brachytherapy without EBRT, which is, to the best of our knowledge, the first such treatment reported in published studies [9]. In 1995, we launched HDR monotherapy with 48 Gy/8 fractions/5 days, and escalated the dose to 54 Gy/9 fractions/5 days the next year and continued it until 2005 eventually treating a total of 119 patients [10–12]. The method we used to determine our dose-fractionation schedule has been previously reported [11].

With a median follow-up of 5.4 years, we achieved a satisfactory biochemical control rate of around 90% for low- and intermediate-risk, and of around 80% for high-risk patients, which may be associated with high BED. On the other hand, the toxicity rate, while acceptable, was not very satisfactory, because some patients experienced Grade 3 and 2 toxicity in spite of an excellent dose distribution of HDR brachytherapy. Specifically, 5% acute and 3% late Grade 3 toxicity occurred in this study cohort, as well as 7.1% each for late Grade 2 gastrointestinal and genitourinary toxicity for the 54 Gy regimen [12]. This first prompted us to reduce the dose of our regimen. In addition, Brenner and Hall in 1999 [14], as well as others later on [15–18], reported a very low α/β ratio for prostate cancer mostly in the range of 1.2–3.1 Gy. Although the real α/β value is still under debate, we assumed 1.5 Gy as the most representative one in this study. Because such α/β values of around 1.5 Gy were significantly lower than estimated in 1995 or 1996 when we had determined the 54 Gy/9 fractions regimen, we began to consider the BED of the 54 Gy regimen as perhaps higher than necessary. The third reason for dose reduction was that our regimen, in comparison to other dose-fractionation regimens reported in the literature (Appendix 1), had a rather high BED of 270 Gy (EQD_{2Gy} = 116 Gy, assuming α/β = 1.5 Gy). The list in Appendix 1 shows that the median BED was 256 Gy (range: 208–299) and the median EQD_{2Gy} = 110 Gy (range: 89–128). We therefore terminated the 54 Gy regimen in 2005 and proceeded to using 45.5 Gy/7 fractions while aiming for a BED of 243 Gy and EQD_{2Gy} of 104 Gy. The fourth and final reason for wanting to make our treatment period shorter was that patients felt the length of the 5-day regimen was inconvenient and made them feel uncomfortable, while it also increased the risk of deep vein thrombosis and infection. We therefore decided to reduce the regimen from 5 days to 4 days.

Thus far, the preliminary results have been favorable and met our expectations. Three-year biochemical control rates for intermediate- and high-risk patients were 96% and 90%, respectively, compared with 93% and 85% for the 54 Gy regimen [12]. No toxicity of Grade 3 or higher was observed with the 45.5 Gy regimen, whereas 5% acute and 3% late Grade 3 toxicity was associated with the 54 Gy regimen. The incidence rate of Grade 2 or higher acute toxicity was significantly lower for the 45.5 Gy than for the 54 Gy (p = 0.026). The Grade 2 late gastrointestinal toxicity rate was 1.6%, which was lower than the 7.1% for the 54 Gy regimen. The Grade 2 late genitourinary toxicity rate was 6.3%, which was comparable to 7.1% for the 54 Gy regimen. Overall, our initial impression is that the dose-reduced regimen of 45.5 Gy/7 fractions

Please cite this article in press as: Yoshioka Y et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: A dose reduction trial. Radiother Oncol (2013), http://dx.doi.org/10.1016/j.radonc.2013.10.015

resulted in toxicity equivalent to or less than that for the 54 Gy/9 fraction regimen without compromising the biochemical control rate.

However, the present study had several limitations. First, the number of patients was as small as 63, and the median follow-up time was only 42 months (range 13–72). These indicate that the presented data are only preliminary, so that longer further follow-up and more patients are needed before any general conclusions can be drawn. Secondly, there should be a selection bias. Because this study was not a randomized controlled trial, a possibility remained that patients with better prognosis tended to be enrolled. In fact, we selected at least a candidate for epidural anesthesia and a patient who agreed to 4-day bed rest. Thirdly, more than half of the patients (59%) received hormone therapy, which might affect favorably on PSA failure-free rate, although the rate of use of hormone therapy was lower in this study than in our previous one (84%) [12]. Lastly, effect of "learning curve" should be considered. When the present study started, we had already treated more than 100 patients in our previous study; therefore, the reduced rate of toxicity seen in this study might be attributable partly to our technical improvement, not only to the de-escalation of BED.

Appendix 1 lists as many data on dose fractionations and their clinical results as we could collect from the literature on HDR brachytherapy used as monotherapy for prostate cancer. We discovered that very few institutions were using HDR monotherapy in the 1990s, so that the publications by these institutions in the 2000s were also very few. In the 2000s, however, the number of institutions that started to use HDR monotherapy increased, and the resultant publications have also been increasing in the 2010s. In these findings we could find some interesting trends. The first is toward a smaller number of fractions and shorter treatment duration. In the 1990s and early 2000s, many institutions started using 4-fraction regimens, for example, 38 Gy/4 fractions [19–22]. However, 3-, 2-, or even 1-fraction regimens are being adopted recently. Zamboglou et al. [23], Hoskin et al. [24], and Barkati et al. [25] used 30–34.5 Gy/3 fractions (10–11.5 Gy per fraction), and Hoskin et al. [24] and Ghilezan et al. [26] 26–27 Gy/2 fractions (13–13.5 Gy per fraction). Prada et al. [27] reported their findings for a 19 Gy/1 fraction regimen. On the basis of the linear-quadratic model and the assumption that the α/β value of prostate cancer was lower than the surrounding normal tissue [14–18,28], it appears that a one-fraction regimen would maximize the therapeutic ratio and at the same time resolve the disadvantages of HDR brachytherapy, that is, hospitalization and needle displacement during the treatment period. However, a one-fraction regimen might, by its very nature, undermine the advantages of fractionation, that is, reoxygenation and redistribution (reassortment). Careful watching should thus be essential for such an exciting new regimen.

The second trend appeared to be that the indication for monotherapeutic HDR brachytherapy is being extended from only low-risk or low- to intermediate-risk to intermediate- and high-risk prostate cancer. While we were the first to describe the indication for low- to high-risk groups, subsequent reports limited their indications to only low- or low- to intermediate-risk patients [19,20,22,29,30]. In this context, some authors insisted that HDR monotherapy was suitable only for low- or low- to intermediate-risk, while a combination of EBRT and HDR brachytherapy was suitable for intermediate- to high-risk patients, thus emulating the scheme for permanent LDR seed implant brachytherapy. However, we insisted that there should be no reason for the addition of EBRT, even for the high-risk group, because HDR brachytherapy could adequately irradiate even extracapsular lesions. The most recent publications include more and more reports on intermediate- to high-risk patients treated with HDR monotherapy. Zamboglou et al. [23], who belong to the same institution as Martin et al. [20] who had included only low- to intermediate-risk prostate cancer, recently reported their findings for HDR monotherapy for a large cohort of 718 patients ranging from low- to high-risk. Hoskin's group [24] is carrying out HDR monotherapy for low- to high-risk patients based on a concept similar to ours, while Rogers et al. [31] did so only for an intermediate-risk group of 284 patients. All these recent studies seem to indicate that there is no reason to limit indication for HDR monotherapy to low-risk patients, while the second trend suggests that such indication is being extended to high-risk patients.

As in our case, many institutions implemented dose escalation for HDR monotherapy. As a result, the biochemical control rates thus obtained were generally satisfactory at approximately 90% (Appendix 1). On the other hand, some Grade 2 or even Grade 3 toxicities were seen. The incidence rate for late Grade 2 genitourinary toxicity reportedly ranged from 0.0% to 59.0%, and that for gastrointestinal toxicity from 0.0% to 13.0%. Some authors reported Grade 3 late toxicities, which are undesirable by any standard. On the assumption of $\alpha/\beta = 3.0$ Gy, BED for normal tissue ranged from 120 to 167 Gy (median 144 Gy), and EQD_{2Gy} from 72 to 100 Gy (median 86 Gy). The above-mentioned toxicity rates may well be associated with such high doses. We anticipate that the next trend, i.e., the third, should be dose reduction with the aim of reducing the toxicity rate without compromising the high biochemical control rate achieved thus far. In other words, we should try to determine the optimal BED and, if possible, the true α/β value for prostate cancer by examining results from various dose-fractionation regimens.

In conclusion, after 10 years' experience with the 54 Gy/9 fractions regimen of HDR brachytherapy as monotherapy, we embarked on a dose-reduction trial with a regimen of 45.5 Gy/7 fractions. In comparison to the 54 Gy/9 fractions regimen, our preliminary results showed an equivalent or lower incidence rate for acute and late toxicities, without compromising the excellent biochemical control rate, so that further studies with more patients and longer follow-up are clearly warranted.

Conflict of interest statement

All authors have indicated that they do not have any conflicts of interest in relation to this work.

Acknowledgments

This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (21791192) and Core-to-Core Program (23003).

Appendix 1. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.10.015.

References

[1] Michalski JM, Bae K, Roach M, et al. Long-term toxicity following 3D conformal radiation therapy for prostate cancer from the RTOG 9406 phase I/II dose escalation study. Int J Radiat Oncol Biol Phys 2010;76:14–22.
[2] Alicikus ZA, Yamada Y, Zhang Z, et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. Cancer 2011;117:1429–37.
[3] Sylvester JE, Grimm PD, Wong J, Galbreath RW, Merrick G, Blasko JC. Fifteen-year biochemical relapse-free survival, cause-specific survival, and overall survival following I-125 prostate brachytherapy in clinically localized prostate cancer: Seattle experience. Int J Radiat Oncol Biol Phys 2011;81:376–81.

Please cite this article in press as: Yoshioka Y et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: A dose reduction trial. Radiother Oncol (2013), http://dx.doi.org/10.1016/j.radonc.2013.10.015

[4] Goldner G, Pötter R, Battermann JJ, et al. Comparison between external beam radiotherapy (70 Gy/74 Gy) and permanent interstitial brachytherapy in 890 intermediate risk prostate cancer patients. Radiother Oncol 2012;103:223–7.
[5] Stone NN, Stone MM, Rosenstein BS, Unger P, Stock RG. Influence of pretreatment and treatment factors on intermediate to long-term outcome after prostate brachytherapy. J Urol 2011;185:495–500.
[6] Dattoli M, Wallner K, True L, Cash J, Sorace R. Long-term outcomes after treatment with brachytherapy and supplemental conformal radiation for prostate cancer patients having intermediate and high-risk features. Cancer 2007;110:551–5.
[7] Galalae RM, Kovacs G, Schultze J, et al. Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 2002;52:81–90.
[8] Mate TP, Gottesman JE, Hatton J, et al. High dose-rate afterloading Ir-192 prostate brachytherapy: feasibility report. Int J Radiat Oncol Biol Phys 1998;41:525–33.
[9] Yoshioka Y, Nose T, Yoshida K, et al. High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys 2000;48:675–81.
[10] Yoshioka Y, Nose T, Yoshida K, et al. High-dose-rate brachytherapy as monotherapy for localized prostate cancer: a retrospective analysis with special focus on tolerance and chronic toxicity. Int J Radiat Oncol Biol Phys 2003;56:213–20.
[11] Yoshioka Y, Konishi K, Oh RJ, et al. High-dose-rate brachytherapy without external beam irradiation for locally advanced prostate cancer. Radiother Oncol 2006;80:62–8.
[12] Yoshioka Y, Konishi K, Sumida I, et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: five-year results of an extreme hypofractionation regimen with 54 Gy in nine fractions. Int J Radiat Oncol Biol Phys 2011;80:469–75.
[13] Konishi K, Yoshioka Y, Isohashi F, et al. Correlation between dosimetric parameters and late rectal and urinary toxicities in patients treated with high-dose-rate brachytherapy used as monotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2009;75:1003–7.
[14] Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys 1999;43:1095–101.
[15] Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys 2001;50:1021–31.
[16] Brenner DJ, Martinez AA, Edmundson GK, et al. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. Int J Radiat Oncol Biol Phys 2002;52:6–13.
[17] Wang JZ, Guerrero M, Li XA. How low is the alpha/beta ratio for prostate cancer? Int J Radiat Oncol Biol Phys 2003;55:194–203.
[18] Miralbell R, Roberts SA, Zubizarreta E, et al. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5969 patients in seven international institutional datasets: $\alpha/\beta = 1.4$ (0.9–2.2) Gy. Int J Radiat Oncol Biol Phys 2012;82:e17–24.
[19] Martinez A, Pataki I, Edmundson G, et al. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. Int J Radiat Oncol Biol Phys 2001;49:61–9.
[20] Martin T, Baltas D, Kurek R, et al. 3-D conformal HDR brachytherapy as monotherapy for localized prostate cancer. A pilot study. Strahlenther Onkol 2004;180:225–32.
[21] Corner C, Rojas AM, Bryant L, et al. A Phase II study of high-dose-rate afterloading brachytherapy as monotherapy for the treatment of localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;72:441–6.
[22] Ghadjar P, Keller T, Rentsch CA, et al. Toxicity and early treatment outcomes in low- and intermediate-risk prostate cancer managed by high-dose-rate brachytherapy as a monotherapy. Brachytherapy 2009;8:45–51.
[23] Zamboglou N, Tselis N, Baltas D, et al. High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: treatment evolution and mature results. Int J Radiat Oncol Biol Phys 2013;85:672–8.
[24] Hoskin P, Rojas A, Lowe G, et al. High-dose-rate brachytherapy alone for localized prostate cancer in patients at moderate or high risk of biochemical recurrence. Int J Radiat Oncol Biol Phys 2012;82:1376–84.
[25] Barkati M, Williams SG, Foroudi F, et al. High-dose-rate brachytherapy as a monotherapy for favorable-risk prostate cancer: a Phase II trial. Int J Radiat Oncol Biol Phys 2012;82:1889–96.
[26] Ghilezan M, Martinez A, Gustason G, et al. High-dose-rate brachytherapy as monotherapy delivered in two fractions within one day for favorable/intermediate-risk prostate cancer: preliminary toxicity data. Int J Radiat Oncol Biol Phys 2012;83:927–32.
[27] Prada PJ, Jimenez I, González-Suárez H, et al. High-dose-rate interstitial brachytherapy as monotherapy in one fraction and transperineal hyaluronic acid injection into the perirectal fat for the treatment of favorable stage prostate cancer: treatment description and preliminary results. Brachytherapy 2012;11:105–10.
[28] Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989;62:679–94.
[29] Demanes DJ, Martinez AA, Ghilezan M, et al. High-dose-rate monotherapy: safe and effective brachytherapy for patients with localized prostate cancer. Int J Radiat Oncol Biol Phys 2011;81:1286–92.
[30] Martinez AA, Demanes J, Vargas C, et al. High-dose-rate prostate brachytherapy: an excellent accelerated-hypofractionated treatment for favorable prostate cancer. Am J Clin Oncol 2010;33:481–8.
[31] Rogers CL, Alder SC, Rogers RL, et al. High dose brachytherapy as monotherapy for intermediate risk prostate cancer. J Urol 2012;187:109–16.

Please cite this article in press as: Yoshioka Y et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: A dose reduction trial. Radiother Oncol (2013), http://dx.doi.org/10.1016/j.radonc.2013.10.015

Hepatology Research

Hepatology Research 2013; 43: 717–727 doi: 10.1111/hepr.12007

Original Article

Dynamic computed tomography appearance of tumor response after stereotactic body radiation therapy for hepatocellular carcinoma: How should we evaluate treatment effects?

Tomoki Kimura,[1] Shigeo Takahashi,[1] Masahiro Kenjo,[1] Ikuno Nishibuchi,[1] Ippei Takahashi,[1] Yuki Takeuchi,[1] Yoshiko Doi,[1] Yuko Kaneyasu,[1] Yuji Murakami,[1] Yoji Honda,[2] Hiroshi Aikata,[2] Kazuaki Chayama[2] and Yasushi Nagata[1]

[1]*Department of Radiation Oncology, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan and* [2]*Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan*

Aim: To evaluate the dynamic computed tomography (CT) appearance of tumor response after stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC) and reconsider response evaluation criteria for SBRT that determine treatment outcomes.

Methods: Fifty-nine patients with 67 tumors were included in the study. Of these, 56 patients with 63 tumors underwent transarterial chemoembolization using lipiodol prior to SBRT that was performed using a 3-D conformal method (median, 48 Gy/four fractions). Dynamic CT scans were performed in four phases, and tumor response was evaluated by comparing tumor appearance on CT prior SBRT and at least 6 months after SBRT. The median follow-up time was 12 months.

Results: The dynamic CT appearance of tumor response was classified into the following: type 1, continuous lipiodol accumulation without early arterial enhancement (26 lesions, 38.8%); type 2, residual early arterial enhancement within 3 months after SBRT (17 lesions, 25.3%); type 3, residual early arterial enhancement more than 3 months after SBRT (19 lesions, 28.4%); and type 4, shrinking low-density area without early arterial enhancement (five lesions, 7.5%). Only two tumors with residual early arterial enhancement did not demonstrate remission more than 6 months after SBRT.

Conclusion: The dynamic CT appearance after SBRT for HCC was classified into four types. Residual early arterial enhancement disappeared within 6 months in most type 3 cases; therefore, early assessment within 3 months may result in a misleading response evaluation.

Key words: dynamic computed tomography appearance, hepatocellular carcinoma, stereotactic body radiation therapy

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is closely associated with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections and the increasing prevalence of viral infections has led to an increased incidence of HCC. The curative therapy for HCC involves surgery including resection or transplantation.[1,2] However, only 10–30% patients initially presenting with HCC would be eligible for surgery either due to liver dysfunction, underlying cirrhosis or presence of multifocal tumors arising from viral infection.[3] For such patients, locoregional therapies such as ablative therapies or transarterial chemoembolization (TACE) are recommended.[1,2] Radiation therapy is a locoregional therapy that can be considered as an alternative to ablation/TACE or when these therapies have failed.[1] Recently, advances in imaging and radiation techniques that deliver high doses of radiation to focal HCC have helped to avoid

Correspondence: Dr Tomoki Kimura, Department of Radiation Oncology, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima City 734-8551, Japan. Email: tkkimura@hiroshima-u.ac.jp

This work was partly presented at the 53rd Annual Meeting of American Society for Therapeutic Radiology and Oncology (ASTRO), Miami, FL, USA, October 1–5 2011.

Conflict of interest: none.

Received 1 July 2012; revision 30 September 2012; accepted 15 October 2012.

© 2012 The Japan Society of Hepatology