Table 4 Outcome of EBRT with or without ILBT for biliary tract cancer

Study (ref. no.)	No. of patients	ILBT	Median OS (mo)	2-year OS (%)	5-year OS (%)	2-year LC (%)	5-year LC (%)
Current study	56	Yes	15	31	16	65	65
(original cohort)	153	No	17	33	7	30	22
Current study	56	Yes	15	31	16	65	65
(propensity-score matched-pair cohort)	56	No	17	40	10	35	29
Shin et al (19)	14	Yes	5	0	-	-	-
	17	No	9	21	-	-	-
Ghafoori et al (20)	8	Yes	15	22	13	-	-
	23	No	11		5	80	-
Schleicher et al (21)	18	Yes	9	15	-	-	-
	12	No	4	-	-	-	-
Alden et al (8)	13	Yes	24	40	-	-	-
	8	No	14	25	-	-	-
Deodato et al (22)	9	Yes	13	-	17	-	-
	5	No	22	-	0	-	-
Takamura et al (14)	93	Yes	12	15	4	45*	18*
Kamada et al (23)	54†	Yes	12	-	6	-	-
Veeze-Kuijpers et al (24)	42	Yes	10	18	-	-	-
Fritz et al (12)	30	Yes	10	18	8	-	-
Foo et al (25)	24	Yes	13	19	14	-	-
Flickinger et al (26)	63	No‡	7	12	-	-	-
Crane et al (27)	52	No§	10	13	-	-	-

Abbreviations: EBRT = external beam radiation therapy; ILBT = intraluminal brachytherapy; LC = local control; OS = overall survival.
* Biliary patency rate.
† 6 patients underwent EBRT alone.
‡ 3 patients underwent ILBT alone, and 9 patients received EBRT and ILBT.
§ 3 patients received EBRT and ILBT.

who underwent both EBRT and ILBT in the original cohort could be assigned to a patient from the 153 of the original cohort who underwent EBRT alone to form matched pairs, so that a new cohort of 112 patients could be generated who were well balanced in terms of sex, age, PS, clinical stage, jaundice, and addition of chemotherapy. Because the number of ILBT− patients was far more than that of ILBT+ patients in the original cohort, we generated another cohort with a 1:2 ratio of patients (56 ILBT+:112 ILBT−) and another 3 cohorts without the respective matching factors of sex, age, and PS. The total of 5 statistical calculations revealed that ILBT had no impact on OS or DSS for RT for unresectable biliary tract cancer, which was the most important finding of this study. The survival curves of the ILBT+ and ILBT− groups were almost identical in terms of OS and DSS (Fig. 2a,b), whereas ILBT showed a significant or marginally significant benefit for LC in all the 5 calculations ($P = .010$, .025, .049, .068, and .094). An additional analysis showed a stronger association with better PS and earlier clinical stage for the ILBT+ patients with long-term LC. This suggests that ILBT may be indicated for the treatment of such patients.

This study has several major limitations. First, it was based on retrospective data, so that, despite patient matching, important differences between the 2 treatment modalities may still exist. It should be especially noted that the dose fractionations for EBRT and ILBT and the dose prescription method of ILBT used in this study were not uniform because of its retrospective nature. This study included only high-dose-rate brachytherapy, so that any conclusions can be applied only to high-dose-rate, not to low-dose-rate, brachytherapy. A further limitation of the study is the lack of specific chemotherapy data on cycles and type, acute and long-term toxicity data, information on biliary duct patency, and information on requirement of palliative interventions (ie, requirement for biliary catheters) after RT. However, we believe that the current study provides significant evidence for identification of the role of ILBT, because our study covered the largest number of patients reported thus far and provides a direct comparison of ILBT+ and ILBT− performed with the best achievable statistical method.

Conclusion

The findings of our propensity-score matched-pair analysis lead us to conclude that ILBT has no discernible impact on OS or DSS for RT for unresectable biliary tract cancer. However, ILBT is associated with better LC, especially for patients with better PS and early clinical stage. Therefore, the role of ILBT should be addressed by other measures than survival benefit, for example, by less toxicity,

prolonged biliary tract patency decreasing the need for further palliative interventions, or patient quality of life.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11-30.
2. Anderson CD, Pinson CW, Berlin J, et al. Diagnosis and treatment of cholangiocarcinoma. *Oncologist* 2004;9:43-57.
3. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55.
4. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med* 2008;27:2037-2049.
5. Isohashi F, Ogawa K, Oikawa H, et al. Patterns of radiotherapy practice for biliary tract cancer in Japan: Results of the Japanese radiation oncology study group (JROSG) survey. *Radiat Oncol* 2013;8:76.
6. Yoshioka Y, Ogawa K, Oikawa H, et al. Factors influencing survival outcome for radiotherapy for biliary tract cancer: A multicenter retrospective study. *Radiother Oncol* 2014;110:546-552.
7. Daines WP, Rajagopalan V, Grossbard ML, et al. Gallbladder and biliary tract carcinoma: A comprehensive update, Part 2. *Oncology (Williston Park)* 2004;18:1049-1060.
8. Alden ME, Mohiuddin M. The impact of radiation dose in combined external beam and intraluminal Ir-192 brachytherapy for bile duct cancer. *Int J Radiat Oncol Biol Phys* 1994;28:945-951.
9. Montemaggi O, Costamagna G, Dobelbower R, et al. Intraluminal brachytherapy in the treatment of pancreas and bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1995;32:437-443.
10. Gonzalez Gonzalez D, Gouma D, Rauws E, et al. Role of radiotherapy, in particular intraluminal brachytherapy, in the treatment of proximal bile duct carcinoma. *Ann Oncol* 1999;10:215-220.
11. Buskirk SJ, Gunderson LL, Schild S, et al. Analysis of failure after curative irradiation of extrahepatic bile duct carcinoma. *Ann Surg* 1991;215:125-131.
12. Fritz P, Branbs H, Schraube P, et al. Combined external beam radiotherapy in intraluminal high-dose-rate brachytherapy on bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1994;29:855-861.
13. Eschelman D, Shapiro M, Bonn J, et al. Malignant biliary duct obstruction: Long-term experience with Gianturco stents and combined-modality radiation therapy. *Radiology* 1996;200:717-724.
14. Takamura A, Saito H, Kamada T, et al. Intraluminal low-dose-rate ^{192}Ir brachytherapy combined with external beam radiotherapy and biliary stenting for unresectable extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 2003;57:1357-1365.
15. Shinchi H, Takao S, Nishida H, et al. Length and quality of survival following external beam radiotherapy combined with expandable metallic stent for unresectable hilar cholangiocarcinoma. *J Surg Oncol* 2000;75:89-94.
16. Fuller CD, Wang SJ, Choi M, et al. Multimodality therapy for locoregional extrahepatic cholangiocarcinoma: A population-based analysis. *Cancer* 2009;115:5175-5183.
17. Shinohara ET, Mitra N, Guo M, et al. Radiotherapy is associated with improved survival in adjuvant and palliative treatment of extrahepatic cholangiocarcinomas. *Int J Radiat Oncol Biol Phys* 2009;74:1191-1198.
18. Shinohara ET, Guo M, Mitra N, et al. Brachytherapy in the treatment of cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2010;78:722-728.
19. Shin HS, Seong J, Kim WC, et al. Combination of external beam irradiation and high-dose-rate intraluminal brachytherapy for inoperable carcinoma of the extrahepatic bile ducts. *Int J Radiat Oncol Biol Phys* 2003;57:105-112.
20. Ghafoori AP, Nelson JW, Willett CG, et al. Radiotherapy in the treatment of patients with unresectable extrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:654-659.
21. Schleicher UM, Staatz G, Alzen G, et al. Combined external beam and intraluminal radiotherapy for irresectable Klatskin tumors. *Strahlenther Onkol* 2002;178:682-687.
22. Deodato F, Clemente G, Mattiucci GC, et al. Chemoradiation and brachytherapy in biliary tract carcinoma: Long-term results. *Int J Radiat Oncol Biol Phys* 2006;64:483-488.
23. Kamada T, Saitou H, Takamura A, et al. The role of radiotherapy in the management of extrahepatic bile duct cancer: An analysis of 145 consecutive patients treated with intraluminal and/or external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 1996;34:767-774.
24. Veeze-Kuijpers B, Meerwaldt JH, Lameris JS, et al. The role of radiotherapy in the treatment of bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1990;18:63-67.
25. Foo ML, Gunderson LL, Bender CE, et al. External radiation therapy and transcatheter iridium in the treatment of extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1997;39:929-935.
26. Flickinger JC, Epstein AH, Iwatsuki S, et al. Radiation therapy for primary carcinoma of the extrahepatic biliary system: An analysis of 63 cases. *Cancer* 1991;68:289-294.
27. Crane C, McDonald K, Bauthty J, et al. Limitations of conventional doses of chemoradiation for unresectable biliary cancer. *Int J Radiat Oncol Biol Phys* 2002;53:969-974.

Journal of Breast Cancer

J Breast Cancer 2014 June; 17(2): 157-160 http://dx.doi.org/10.4048/jbc.2014.17.2.157

ORIGINAL ARTICLE

Effects of Geometrical Uncertainties on Whole Breast Radiotherapy: A Comparison of Four Different Techniques

Naoki Nakamura, Osamu Takahashi[1], Minobu Kamo[2], Shogo Hatanaka, Haruna Endo, Norifumi Mizuno, Naoto Shikama[3], Mami Ogita, Kenji Sekiguchi

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

Purpose: The purpose of this study was to quantify the target coverage, homogeneity, and robustness of the dose distributions against geometrical uncertainties associated with four whole breast radiotherapy techniques. **Methods:** The study was based on the planning-computed tomography-datasets of 20 patients who underwent whole breast radiotherapy. A total of four treatment plans (wedge, field-in-field [FIF], hybrid intensity-modulated radiotherapy [IMRT], and full IMRT) were created for each patient. The hybrid IMRT plans comprised two opposed tangential open beams plus two IMRT beams. Setup errors were simulated by moving the beam isocenters by 5 mm in the anterior or posterior direction. **Results:** With the original plan, the wedge technique yielded a high volume receiving ≥107% of the prescription dose (V_{107}; 7.5%±4.2%), whereas the other three techniques yielded excellent target coverage and homogeneity. A 5 mm anterior displacement caused a large and significant increase in the V_{107} (+5.2%±4.1%, $p<0.01$) with the FIF plan, but not with the hybrid IMRT (+0.4%±1.2%, $p=0.11$) or full IMRT (+0.7%±1.8%, $p=0.10$) plan. A 5-mm posterior displacement caused a large decrease in the V_{95} with the hybrid IMRT (-2.5%±3.7%, $p<0.01$) and full IMRT (-4.3%±5.1%, $p<0.01$) plans, but not with the FIF plan (+0.1%±0.7%, $p=0.74$). The decrease in V_{95} was significantly smaller with the hybrid IMRT plan than with the full IMRT plan ($p<0.01$). **Conclusion:** The FIF, hybrid IMRT, and full IMRT plans offered excellent target coverage and homogeneity. Hybrid IMRT provided better robustness against geometrical uncertainties than full IMRT, whereas FIF provided comparable robustness to that of hybrid IMRT.

Key Words: *Breast neoplasms, Intensity-modulated radiotherapy*

INTRODUCTION

The avoidance of hot spots throughout the breast volume is difficult with external whole breast radiotherapy using conventional forward wedge planning [1,2]. For this reason, intensity-modulated radiotherapy (IMRT) is gradually replacing wedge planning [3]. IMRT provides excellent dose homogeneity throughout the breast volume [4]. One disadvantage of IMRT is that the IMRT plans might be more susceptible to setup and motion uncertainties [5-9]. The intact breast flash is used to compensate for motion in the anteroposterior direction in glancing open fields; however, flash cannot be easily achieved when using the IMRT inverse-planning technique.

The field-in-field (FIF) technique is a forward-planning intensity-modulating technique [10,11] in which fields are created by strategically placing multileaf collimator leaves in hot spots. FIF plans can incorporate fields with the breast flash and thus might reduce the effects of geometrical uncertainties. Another possible solution to reduce the effects of geometrical uncertainties would be the use of a hybrid technique that incorporates a combination of glancing open fields and inverse-planned IMRT beams [5].

The purpose of this study was to quantify the target coverage, homogeneity, and robustness of the dose distributions against geometrical uncertainties associated with four whole breast radiotherapy techniques (wedge, FIF, hybrid IMRT, and full IMRT).

Correspondence to: Naoki Nakamura
Department of Radiation Oncology, St. Luke's International Hospital, 9-1 Akashi-cho, Chuou-ku, 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 54th Annual Meeting of the American Society for Radiation Oncology (ASTRO) at Boston, MA, October 28–31, 2012.

Received: November 12, 2013 **Accepted:** April 18, 2014

http://ejbc.kr | pISSN 1738-6756
eISSN 2092-9900

METHODS

Patients and scans

This study was approved by the Institutional Review Board (11-R190). The planning computed tomography datasets of 20 patients who underwent whole breast radiotherapy at St. Luke's International Hospital (10 with left-sided and 10 with right-sided cancer) formed the basis of this study. Computed tomography was performed without breath holding by using a LightSpeed RT 16 (GE Healthcare, Fairfield, USA) helical scanner with a 5-mm slice thickness.

Treatment planning

A total of four treatment plans (wedge, FIF, hybrid IMRT, and full IMRT) were created for each patient by using the Pinnacle^3 version 9.0 planning software package (Philips Medical, Amsterdam, The Netherlands). Adaptive convolution was the selected calculation algorithm. The clinical target volume (CTV) was defined as the ipsilateral whole breast. The planning target volume was defined as the CTV plus a surrounding 0.8- to 1.5-cm margin. The target volume for evaluation (TV_EV) was defined by subtracting the areas within 5 mm of the skin or lung from the whole breast.

All four plans used two opposed tangential 4 to 6 MV beams set at the same angles. The wedge plans comprised two opposed tangential open beams with wedges. The FIF plans comprised two opposed tangential open beams plus 2 to 4 reduction fields at the same angles. Plan optimization was performed in a forward fashion. The details of the FIF plans used in our institution have been reported previously [11]. The hybrid IMRT plans comprised two opposed tangential open beams plus two IMRT beams set at the same angles. The open beams contributed 90% of the dose, whereas the inversely optimized IMRT beams contributed 10%. For IMRT, direct-machine parameter optimization was performed to set the dose to the whole TV_EV between 95% and 107% of the prescribed dose. The full IMRT plans comprised 100% segments that had been inversely optimized. The plans were normalized such that 50% of the TV_EV received a total of 50 Gy in 2-Gy fractions for both the hybrid IMRT and full IMRT plans, whereas for the wedge and FIF plans, doses were prescribed to the beam isocenters.

Setup errors were simulated by moving the beam isocenters by 5 mm in the anterior or posterior direction.

Statistical analysis

The target coverage and homogeneity were assessed according to the volume of the TV_EV receiving ≥95% of the prescription dose (V_{95}), V_{107}, and the mean dose to the TV_EV. The doses to the organs at risk were assessed as the V_{20} of both lungs, mean dose to both lungs, V_{30} of the heart, and mean dose to the heart. The V_{30} of the heart and mean heart dose were assessed in the patients with left-sided cancer.

We additionally measured the time required to deliver 2 Gy with each technique via simulation with a phantom.

We used the SPSS version 20 package (SPSS Inc., Chicago, USA) for statistical analysis. Differences were deemed significant when the two-tailed p-values were less than 0.05.

RESULTS

Target coverage and homogeneity

Table 1 shows the target coverage and homogeneity values achieved with the four techniques according to the original plan. The wedge technique yielded a high V_{107} (7.5%±4.2%) whereas the other three techniques provided excellent target coverage and homogeneity. Table 2 shows the differences in target coverage and homogeneity from the original plan in response to moving the beam isocenters by 5 mm in the anterior or posterior direction.

A 5-mm displacement in the anterior direction caused a large increase in the V107 (+5.2%±4.1%, $p<0.01$) with the FIF plan, whereas no significant increases were observed with the hybrid IMRT (+0.4%±1.2%, $p=0.11$) or full IMRT (+0.7%±1.8%, $p=0.10$) plan. A 5-mm displacement in the posterior direction caused a large decrease in the V_{95} with the hybrid IMRT (-2.5%±3.7%, $p<0.01$) and full IMRT (-4.3%±5.1%, $p<0.01$) plans, whereas no significant decrease was noted with the FIF plan (+0.1%±0.7%, $p=0.74$). The decrease in the V_{95} was significantly smaller with the hybrid IMRT plan than with the full IMRT plan ($p<0.01$).

Doses to the organs at risk

Table 3 shows the doses provided to both lungs and the heart when using the four techniques according to the original plan. Table 4 shows the differences in these values from the original plan after moving the beam isocenters by 5 mm

Table 1. Target coverage and homogeneity with the four techniques in the original plan

Technique	D_{mean} (Gy)	V_{95} (%)	V_{107} (%)
Wedge	51.4±0.4	99.2±0.5	7.5±4.2
FIF	51.0±0.4	97.6±1.3	0.2±0.4
Hybrid IMRT	50.2±0.4	98.4±0.3	0.1±0.4
Full IMRT	50.2±0.4	98.4±0.4	0.1±3.3

Data are presented as mean±SD.
D_{mean}=mean dose of the target volume for evaluation (TV_EV); V_x=the volume of the TV_EV receiving by X% of the prescription dose or greater; FIF=field-in-field; IMRT=intensity-modulated radiotherapy.

http://dx.doi.org/10.4048/jbc.2014.17.2.157

Table 2. Differences in the target coverage and homogeneity from the original plan by moving beam isocenters by 5 mm in the anterior or posterior direction

Technique	D_{mean} (Gy)	*p*-value	V_{95} (%)	*p*-value	V_{107} (%)	*p*-value
Anterior direction						
Wedge	+0.2±0.1	<0.01*	+0.1±0.1	<0.01*	+1.5±1.1	<0.01*
FIF	+0.1±0.2	0.01*	-0.7±0.8	<0.01*	+5.2±4.1	<0.01*
Hybrid IMRT	+0.4±0.2	<0.01*	-0.5±0.8	<0.01*	+0.4±1.2	0.11
Full IMRT	+0.4±0.2	<0.01*	-1.0±1.0	<0.01*	+0.7±1.8	0.10
Posterior direction						
Wedge	-0.2±0.1	<0.01*	-0.2±0.2	<0.01*	-1.4±0.9	<0.01*
FIF	-0.2±0.2	<0.01*	+0.1±0.7	0.74	0.0±0.4	0.69
Hybrid IMRT	-0.5±0.3	<0.01*	-2.5±3.7	<0.01*	0.0±0.1	0.65
Full IMRT	-0.6±0.3	<0.01*	-4.3±5.1	<0.01*	-0.1±0.2	0.38

Data are presented as mean±SD.
D_{mean} = mean dose of the target volume for evaluation (TV_EV); V_x = the volume of the TV_EV receiving by X% of the prescription dose or greater; FIF = field-in-field; IMRT = intensity-modulated radiotherapy.
*Indicate statistically significant differences.

Table 3. Dose for the bilateral lungs and heart with the four techniques in the original plan

Technique	Bilateral lungs		Heart	
	V_{20} (%)	Mean (Gy)	V_{30} (%)	Mean (Gy)
Wedge	8.9±2.1	5.2±2.1	1.4±1.7	3.1±2.2
FIF	8.7±2.1	4.8±1.5	1.3±1.6	2.1±1.1
Hybrid IMRT	8.6±2.1	4.7±1.5	1.2±1.4	2.0±1.0
Full IMRT	7.0±2.4	3.6±1.1	0.3±0.4	1.4±0.4

Data are presented as mean±SD.
V_x = the volume of the organ receiving by X% of the prescription dose or greater; FIF = field-in-field; IMRT = intensity-modulated radiotherapy.

Table 4. Differences in the dose for the bilateral lungs and heart from the original plan by moving beam isocenters by 5 mm in the anterior or posterior direction

Technique	Bilateral lungs		Heart	
	V_{20} (%)	Mean (Gy)	V_{30} (%)	Mean (Gy)
Anterior direction				
Wedge	-1.8±0.3	-0.9±0.2	-0.8±0.9	-1.0±0.9
FIF	-1.8±0.3	-0.9±0.2	-0.8±0.9	-0.6±0.4
Hybrid IMRT	-1.8±0.3	-0.9±0.2	-0.8±0.8	-0.6±0.4
Full IMRT	-1.6±0.3	-0.8±0.2	-0.3±0.3	-0.4±0.2
Posterior direction				
Wedge	1.9±0.4	0.9±0.2	1.4±1.2	1.2±0.9
FIF	1.9±0.3	0.9±0.2	1.4±1.2	0.9±0.5
Hybrid IMRT	1.9±0.3	0.9±0.2	1.3±1.2	0.9±0.5
Full IMRT	1.7±0.3	0.8±0.2	0.8±0.6	0.6±0.3

Data are presented as mean±SD.
V_x = the volume of the organ receiving by X% of the prescription dose or greater; FIF = field-in-field; IMRT = intensity-modulated radiotherapy.

in the anterior or posterior direction. For all four techniques, acceptable outcomes were obtained for all parameters, although a more favorable tendency was observed with the full IMRT plan.

Table 5. Delivery time for 2 Gy with each technique

Technique	Delivery time (sec)
Wedge	153±14
FIF	129±11
Hybrid IMRT	170±18
Full IMRT	140±21

Data are presented as mean±SD.
FIF = field-in-field; IMRT = intensity-modulated radiotherapy.

Delivery time

Table 5 shows the time required to deliver 2 Gy using each technique. The FIF delivery time was the shortest, whereas the hybrid IMRT delivery time was the longest. However, the absolute differences in the delivery times were small.

DISCUSSION

Our results showed that hybrid IMRT was superior to full IMRT in terms of robustness against geometrical uncertainties, thus corroborating the findings of a previous investigation [5]. The breast flash was not implemented in the optimization routine for the inverse planning technique, leading to underdosage near the skin under posterior displacement conditions. In this sense, the full IMRT technique was suboptimal for whole breast radiotherapy.

However, hybrid IMRT offered excellent target coverage and homogeneity comparable to that of full IMRT. Theoretically, hybrid IMRT techniques should provide worse dose distributions in exchange for better robustness against geometrical uncertainties, as the contribution from the inversely optimized IMRT beams is reduced. We used an IMRT beam contribution of only 10% to achieve better robustness against geo-

metrical uncertainties and found that this 10% contribution was sufficient to yield excellent target coverage and homogeneity for whole breast radiotherapy and to provide better robustness against geometrical uncertainties, given the high percentage of glancing open fields.

We found that the FIF technique also offered excellent target coverage and homogeneity. The disadvantage with FIF was the generation of considerable hot spots under anterior displacement conditions. The advantage of FIF was its strong robustness with posterior displacement. Given these features, we consider the FIF technique as an alternative to hybrid IMRT.

The wedge technique showed good robustness against geometrical uncertainties. However, this technique yielded a high V_{107}, which would likely increase the risk of severe dermatitis.

Regarding the doses to the lungs and heart, we observed similar, acceptable outcomes both with the original plan and in terms of the robustness against geometrical uncertainties for all four techniques, although a more favorable tendency was observed with full IMRT.

We also evaluated the delivery time with each technique. The delivery times for all four techniques were similarly short. We therefore do not consider the delivery time to be an important factor in technique selection.

A limitation of our investigation is that only a small series of Japanese patients were evaluated. The breasts investigated in this study might be smaller than the global average. A focus on patients with larger breasts and possibly larger geometrical uncertainties might yield different findings. Another limitation is that only anterior-posterior displacement setup errors were evaluated; however, geometric uncertainties include displacement in the left-right, craniocaudal, and anteroposterior directions. Nevertheless, we believe that the outcomes of this study will offer some guidance to clinicians in a field in which data are relatively lacking.

In conclusion, the FIF, hybrid IMRT, and full IMRT plans offered excellent target coverage and homogeneity. Hybrid IMRT was superior to full IMRT in terms of robustness against geometrical uncertainties, whereas FIF provided comparable robustness to that of hybrid IMRT.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Aref A, Thornton D, Youssef E, I Ie T, Tekyi-Mensah S, Denton L, et al. Dosimetric improvements following 3D planning of tangential breast irradiation. Int J Radiat Oncol Biol Phys 2000;48:1569-74.
2. Buchholz TA, Gurgoze E, Bice WS, Prestidge BR. Dosimetric analysis of intact breast irradiation in off-axis planes. Int J Radiat Oncol Biol Phys 1997;39:261-7.
3. Smith BD, Pan IW, Shih YC, Smith GL, Harris JR, Punglia R, et al. Adoption of intensity-modulated radiation therapy for breast cancer in the United States. J Natl Cancer Inst 2011;103:798-809.
4. Harsolia A, Kestin L, Grills I, Wallace M, Jolly S, Jones C, et al. Intensity-modulated radiotherapy results in significant decrease in clinical toxicities compared with conventional wedge-based breast radiotherapy. Int J Radiat Oncol Biol Phys 2007;68:1375-80.
5. van Mourik A, van Kranen S, den Hollander S, Sonke JJ, van Herk M, van Vliet-Vroegindeweij C. Effects of setup errors and shape changes on breast radiotherapy. Int J Radiat Oncol Biol Phys 2011;79:1557-64.
6. Jain P, Marchant T, Green M, Watkins G, Davies J, McCarthy C, et al. Inter-fraction motion and dosimetric consequences during breast intensity-modulated radiotherapy (IMRT). Radiother Oncol 2009;90:93-8.
7. Fan Y, Nath R. Intensity modulation under geometrical uncertainty: a deconvolution approach to robust fluence. Phys Med Biol 2010;55:4029-45.
8. Schwarz M, Van der Geer J, Van Herk M, Lebesque JV, Mijnheer BJ, Damen EM. Impact of geometrical uncertainties on 3D CRT and IMRT dose distributions for lung cancer treatment. Int J Radiat Oncol Biol Phys 2006;65:1260-9.
9. Bos LJ, van der Geer J, van Herk M, Mijnheer BJ, Lebesque JV, Damen EM. The sensitivity of dose distributions for organ motion and set-up uncertainties in prostate IMRT. Radiother Oncol 2005;76:18-26.
10. de la Torre N, Figueroa CT, Martinez K, Riley S, Chapman J. A comparative study of surface dose and dose distribution for intact breast following irradiation with field-in-field technique vs. the use of conventional wedges. Med Dosim 2004;29:109-14.
11. Nakamura N, Hatanaka S, Shikama N, Akahane K, Sekiguchi K. Quantification of cold spots caused by geometrical uncertainty in field-in-field techniques for whole breast radiotherapy. Jpn J Clin Oncol 2011;41:1127-31.

http://dx.doi.org/10.4048/jbc.2014.17.2.157

Columbia International Publishing
American Journal of Breast Cancer Research
(2014) Vol. 1 No. 1 pp. 1-8

Research Article

Preliminary Results from a Multi-center Prospective Study (JROSG 05-5) on Postoperative Radiotherapy for Patients with High-risk Ductal Carcinoma in situ with Involved Margins or Margin Widths 1 mm or less than

Naoto Shikama[1*], Kenji Sekiguchi[2], Naoki Nakamura[2], Hiroshi Sekine[3], Yuko Nakayama[4], Kazufumi Imanaka[5], Takeshi Akiba[6], Masahiko Aoki[7], Yoshiomi Hatayama[7], Etsuko Ogo[8], Yoshikazu Kagami[9], Miho Kawashima[10], and Kumiko Karasawa[11]

Received 25 December 2013; Published online 8 February 2014

Abstract

Purpose: This prospective study aimed to evaluate the effectiveness of postoperative radiotherapy (PORT) consisting of whole breast irradiation followed by boost irradiation in patients with high-risk ductal carcinoma in situ (DCIS) with margin widths less than 1 mm.

Materials and Methods: A multi-center phase II study (Japanese Radiation Oncology Study Group: JROSG 05-5) was conducted to evaluate the effectiveness of PORT. PORT consisted of whole breast irradiation (50 Gy/25 fractions) followed by boost irradiation (10 Gy/5 fractions) using electron beams for patients with high-risk DCIS. Eligibility criteria were as follows: 1) DCIS without an invasive carcinoma component, 2) age between 20 and 80 years, 3) involved margins or margin widths less than 1 mm, 4) refusal of re-resection, 5) performance status of 0–2, and 6) written informed consent. The primary endpoint was ipsilateral breast tumor recurrence (IBTR), and secondary endpoints were overall survival, relapse-free survival, recurrence patterns, and adverse events.

*Corresponding author e-mail: nshikama0525@gmail.com
1 Department of Radiation Oncology, Saitama Medical University, International Medical Center, Saitama, Japan
2 Department of Radiation Oncology, St Luke's International Hospital
3 Department of Radiology, The Jikei University Third Hospital
4 Department of Radiation Oncology, Kanagawa Cancer Center
5 Department of Radiology, Nishikobe Medical Center
6 Department of Radiation Oncology, Tokai University
7 Department of Radiology, Hirosaki University School of Medicine and Hospital
8 Department of Radiation Oncology, Kurume University Hospital
9 Department of Radiation Oncology, Showa University Hospital
10 Department of Radiology, Dokkyo Medical University, Koshigaya Hospital
11 Research Center for Charged Particle Therapy, National Institute of Radiological Sciences

Results: Thirty-seven patients from 12 institutions were enrolled from January 2007 to May 2009. Median follow-up time was 45 months (range, 27–64 months). The median pathological tumor size was 2.5 cm (range, 0.3–8.5 cm). Twenty-one patients had close margins, and 16 had involved margins. Four-year IBTR, overall survival, and relapse-free survival rates were 3% (95% confidence interval (CI): 0–20), 97% (95% CI: 82–100), and 94% (95% CI: 77–99), respectively.

Conclusions: Our preliminary results suggest that this PORT schedule may be promising for patients with high-risk DCIS. However, to make any definitive conclusions, a longer follow-up time is required.

Keywords: Ductal carcinoma in situ; Breast cancer; Margin width; Radiotherapy; Breast conservation

1. Introduction

Ductal carcinoma in situ (DCIS) is a slow growing tumor of the breast tissue that is less aggressive than other forms of cancer. Many such tumors require radiotherapy or surgical treatment (Schwartz, G., et al., 1999, Punglia, R.S., et al., 2013). Mammography screenings increase the opportunity for treatment of patients with DCIS (Ernster, V., et al. 1996). In the United States, by 2013, approximately 64,640 new DCIS diagnoses will be made, constituting approximately 22% of all new breast cancers (Silgel, R., et al., 2013). Breast conserving therapy, including partial resection followed by breast irradiation, has been one of the standard treatments for DCIS (Punglia, R.S., et al., 2013). Several randomized clinical trials have demonstrated that postoperative radiotherapy (PORT) decreases the risk of ipsilateral breast tumor recurrence (IBTR) (Fisher, B., et al., 1993; Fisher, B., et al., 1998; Houghton, J., et al., 2003; Julien, J., et al., 2000). However, these randomized trials have mainly included low-risk patients with negative surgical margins. There has been little evidence supporting treatment strategies for patients with high-risk DCIS and either a positive surgical margin or a narrow distance between surgical margins and tumor cells.

Silverstein et al. (1996) developed a prognostic model that included tumor size, margin width, and pathological classification (the Van Nuys Prognostic Index; VNPI). Patients with high VNPI scores (e.g., 8 or 9) showed high rates of IBTR, after receiving PORT. In contrast, the eight-year IBRT rate among patients with low VNPI scores (e.g., 3 or 4) was low regardless of whether or not PORT was used (100% vs. 97%). Silverstein et al. (1999) reported that patients with tumor margin widths less than 1 mm could benefit from PORT, with an eight-year IBTR rate of approximately 30%. However, this retrospective study included a variety of PORT schedules. Few prospective studies have evaluated the role of PORT exclusively for high-risk DCIS, and a maximally-effective treatment schedule has not yet been established. The present prospective study aimed to evaluate the effectiveness of PORT consisting of whole breast irradiation followed by boost irradiation in patients with high-risk DCIS and tumor margin widths less than 1 mm.

2. Materials and Methods

A multi-center phase II study (Japanese Radiation Oncology Study Group: JROSG 05-5) was conducted to evaluate the effectiveness of PORT consisting of tangential whole breast irradiation (50 Gy/25 fractions) followed by boost irradiation (10 Gy/5 fractions) of the tumor bed using electron beams for patients with high-risk DCIS. Patients were eligible for inclusion in the study if

they: 1) had DCIS without an invasive carcinoma component, 2) were between 20 and 80 years of age, 3) were diagnosed as having involved margins or margin widths less than 1 mm after pathological evaluation using 5 mm thick specimens, 4) refused re-resection, 5) had a performance status of 0–2, and 6) provided written informed consent. Exclusion criteria were: 1) bilateral breast cancers, 2) diffuse calcification, 3) multiple tumors, 4) macroscopic residual tumor, 5) positive axillary lymph node metastases, 6) past history of chest irradiation, 7) collagen vascular disease, 8) pregnancy, 9) active double cancer, 10) mental disorders, 11) uncontrolled diabetes, 12) uncontrolled hypertension, and 13) cardiac disease.

Radiation Treatment Planning

All patients were placed in the supine position, and underwent computed tomography (CT) as part of the radiation treatment planning. CT scanning was performed, with slices extended to completely cover the bilateral whole breast, lungs, heart, and lower neck. No respiratory control was used. All patient procedures were planned using three-dimensional conformal radiotherapy (3D-CRT) treatment planning software. To correctly evaluate heterogeneous tissue density, the analytical anisotropic algorithm, a superposition algorithm, convolution algorithm, or AAA algorithm was used. Whole breast irradiation was comprised of tangential beams using 4 or 6 MV photons. Simulation planning was used to minimize radiation to at-risk organs, and to modify homogeneous doses to fit target volumes using a wedge filter. Beam weights, beam angles, and wedge angles were manually optimized. A total dose of 50 Gy in 25 fractions for whole breast irradiation was defined at the reference point (isocenter). The isocenter was placed in the center of the radiation field or vicinity. The electron beam width for boost irradiation of the tumor bed was determined according to surgical clips, surgical cavity, and pathological findings (e.g., 3 cm-margin). Appropriate electron beam energy was selected according to the depth of the tumor bed.

Endpoints and Statistical Analyses

The primary endpoint was the IBTR, and secondary endpoints were overall survival (OS), relapse-free survival (RFS), recurrence patterns, and adverse events. IBTR was defined as recurrence (invasive carcinoma or DCIS) in the ipsilateral irradiated breast. OS time was defined as the time from registration to death (due to any cause). RFS time was defined as the time from registration to treatment failure (in the ipsilateral breast, axillary node, or at a distant site) or death (due to any cause). Toxicities were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The five-year estimated IBTR rate was projected as 20% and the low five-year IBTR rate threshold was set at 45%. It was estimated that a sample of 36 patients was required, with a one-sided alpha of 0.05 and a statistical power of 90% (assuming several patients would be lost to follow-up). Kaplan-Meier methods were used to estimate IBTR, OS, and RFS. All enrolled patients were included in the primary endpoint assessment (an intention-to-treat analysis).

3. Results

This protocol concept was accepted in October 2005, and the full protocol was accepted in August 2006 by the executive Japanese Radiation Oncology Study Group (JROSG) committee. Thirty-seven patients from 12 institutions were enrolled from January 2007 to May 2009. The median patient follow-up time was 45 months (range, 27–64 months), median patient age was 52 years (range,

33–78 years), and median pathological tumor size was 2.5 cm (range, 0.3–8.5 cm). Patient characteristics are shown in Table 1.

Table 1 Patient Characteristics

	n (%)	
Age (years)		Median 52 (33–78)
30–39	3(8)	
40–49	11(30)	
50–59	14(38)	
60–70	6(16)	
≥70	3(8)	
Pathological diameter (cm)		Median 2.5 (0.3–8.5)
≤1.9	15(41)	
2–3.9	6(16)	
4–5.9	7(19)	
≥6	9(24)	
Estrogen receptor		
Positive	26(70)	
Negative	7(19)	
Unknown	4(11)	
Progesterone receptor		
Positive	22(60)	
Negative	11(30)	
Unknown	4(10)	
Margin status		
Close margin	16(43)	
Involved margin	21(57)	

Sixteen patients had close margins, and 21 had involved margins. All patients received PORT per-protocol, and no patient interrupted PORT. Fourteen (38%) patients received adjuvant hormonal therapy.

The four-year IBTR, OS, and RFS rates were 3% (95% confidence interval [CI]: 0–20), 97% (95% CI: 82–100), and 94% (95% CI: 77–99), respectively (Figure 1).

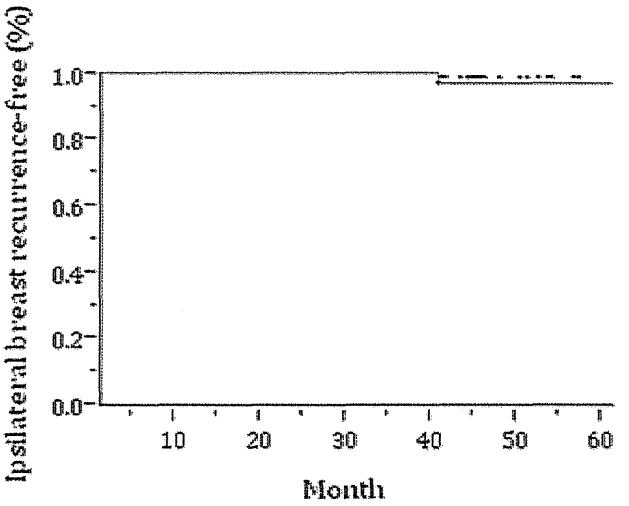

Fig 1. Ipsilateral Breast Tumor Recurrence-Free Survival Curve

One patient with close margins, who received adjuvant tomoxifen, developed local recurrence at the original site after 39 months. She underwent a salvage mastectomy, and the pathological diagnosis was DCIS without an invasive carcinoma component. One patient died of colon cancer 28 months after registration, without experiencing breast cancer recurrence. No recurrence events were identified in regional lymph nodes or distant sites, and no severe adverse events (Grade 3 or 4) have been reported to date.

4. Discussion

The current standard of care for patients with DCIS includes mastectomy and breast conserving therapy. The Canadian population-based registries demonstrated that the frequency of mastectomy for patients with DCIS decreases yearly, and that only 19% of DCIS patients underwent mastectomy between 1990 to 2000 (Rakovitch, E., et al., 2003). Mastectomy is still considered a standard treatment for patients with diffuse infiltrative disease, large tumors, or positive surgical margins after repeated resection. The incidence of axillary lymph node metastases is very low, and the roles of axillary lymph node dissection and sentinel lymph node biopsy have not yet been established (Cox, C., et al., 2001). If the existence of invasive carcinoma is suspected, however, axillary management, including axillary lymph node dissection and sentinel lymph node biopsy, is considered.

There remains room for discussion regarding whether all patients with DCIS should be treated. Although it is uncertain what the probability of progression is, it has been suggested that the lifetime risk of DCIS progression is considerably less than 50% (Welch, H.G. et al., 2008). Studies have also indicated that PORT after partial resection reduces the IBTR rate by approximately 60% (Kuerer, H.M., et al., 2009). One half of patients who experience local recurrence after breast conserving therapy have invasive carcinoma, and other has non-invasive carcinoma. There have been no reports showing that the omission of PORT increases distant metastases or decrease OS.

The main goal of DCIS management is to reduce the risk of progression to invasive carcinoma (Punglia, R.S., et al., 2013), and the secondary goal is to avoid patients having to undergo salvage mastectomy. However, in the United States, population-based analyses have revealed that, among patients who receive partial resection for DCIS, approximately half do not receive PORT, with substantial variation in the use of this treatment (Punglia, R.S., et al., 2013).

Silverstein et al. (1996) developed the VNPI model for patients with DCIS, which includes tumor size, surgical margin width, and pathological findings. Dunne et al. (2009) conducted a systematic review and reported that a margin threshold of 2 mm seemed to be as good as a larger margin when breast conserving surgery for DCIS is combined with PORT. Wang et al. (2012) conducted a meta-analysis of margin threshold for patients with DCIS. This study reported that, as compared with a negative tumor margin greater than 2 mm, a negative tumor margin of at least 10 mm was associated with a lower risk of IBTR (odds ratio(OR)=0.46, 95% CI: 0.29–0.69). Silverstein et al. (1999) reported that patients with tumor margin widths less than 1 mm could benefit from PORT, with an eight-year IBTR probability of 30% and approximately 80% of recurrence developing within three years. This retrospective study included various radiotherapy schedules (e.g., dose of whole breast, 40 to 50 Gy), with boost irradiation (16 to 20 Gy) being delivered to the tumor bed via brachytherapy or electron beam therapy. Only a few prospective studies have evaluated the role of PORT exclusively in high-risk patients with DCIS. The preliminary results of this prospective study showed that the four-year IBTR rate was only 3% after PORT. This preliminary result indicated that PORT, consisting of tangential whole breast irradiation (50 Gy/25 fractions) followed by boost irradiation (10 Gy/5 fractions) of the tumor bed was a promising schedule for high-risk patients with DCIS.

The limitations of this study are its small sample size and short follow-up time. In addition, a central pathological review has not been conducted. Although a central pathological review system was not established prior to this prospective trial, it was determined that the method of pathological evaluation of resection samples would be conducted using a 5 mm thick slice. This technique is believed to provide accurate pathological evaluation of tumor extension and margin width.

5. Conclusions

Our preliminary results suggest that this radiotherapy schedule could be promising for patients with high-risk DCIS. A longer follow-up time is required, however, to make any definitive conclusions.

Acknowledgements

This study was presented in part at the 55th Annual Meeting of the American Society for Radiology Oncology, Atlanta, GA, in October 2013. The authors are grateful to Mrs. Y. Asazawa and Mrs. K. Saito for technical assistance. This study was supported by a Health and Labor Sciences Research Grant (H24-007, H22-018), a Grant-in-Aid for Cancer Research (23-A-21), and a Grant-in-Aid for Scientific Research: "Third term comprehensive control research for cancer (H22-043, H23-007)" from the Ministry of Health, Labor, and Welfare of Japan.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References

Cox, C., Nguyen K., and Gray, R. 2001. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): Why map DCIS? Am Surg 67, 513.

Dunne, C., Burke, J.P., Marrow, M., and Kell, M.R. 2009. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. J Clin Oncol 27(10), 1615-1620. http://dx.doi.org/10.1200/JCO.2008.17.5182

Ernster, V. L., Barclay, J., Kerlikowske, K., Grady, D., and Henderson, C. 1996. Incidence of and treatment for ductal carcinoma in situ of the breast. JAMA 275, 913-918. http://dx.doi.org/10.1001/jama.1996.03530360023033

Fisher, B., Dignam, J., Wolmark, N., Mamounas, E., Costantino, J., Poller, W., Fisher, E. R., Wickerham, D. L., Deutsch, M., Margolese, R., Dimitrov, N., Kavanah, M. 1998. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol 16(2), 441-452.

Fisher, B., Costantino, J., Redmond, C., Fisher, E., Margolese, R., Dimitrov, N., Wolmark, N., Wickerham, D. L., Deutsch, M., Ore, L., Mamounas, E., Poller, W., and Kavanah, M. 1993. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. N Engl J Med 328(22), 1581-1586. http://dx.doi.org/10.1056/NEJM199306033282201

Houghton, J., George, W. and Cuzick, J. 2003. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomized controlled trial. Lancet 362, 95-102. http://dx.doi.org/10.1016/S0140-6736(03)13859-7

Julien, J. P., Bijker, N., Fentiman, I. S., Peterse, J. L., Delledonne, V., Rouanet, P., Avril, A., Sylvester, R., Mignolet, F., Bartelink, H., Van Dongen, J. A. 2000. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 355, 528-533. http://dx.doi.org/10.1016/S0140-6736(99)06341-2

Kuerer, H.M., Albrracin C.T., Yang, W.T., Cardiff, R.D., Brewster, A.M., Symmans, W.F., Hylton, N.M., Middleton, L.P., Krishnamurthy, S., Perkins, G.H., Babriera, G., Edgerton, M.E., Czerniecki, B.J., Arun, B.K., and Hortobagyi, G.N. 2009. J Clin Oncol 27(2), 279-288. http://dx.doi.org/10.1200/JCO.2008.18.3103

Punglia, R.S., Schnitt, S.J., Weeks, J.C. 2013. Treatment of ductal carcinoma in site after excision: would a prophylactic paradigm be more appropriate? J Natl Cancer Inst 105, 1527-1533. http://dx.doi.org/10.1093/jnci/djt256

Rakovitch, E., Tatla, R., Paszat, L., Hanna, W., Goel, V. 2003. Predictors of axillary node dissection in ductal carcinoma in situ: A population-based analysis. Int J Radiat Oncol Biol Phys 57(2), S240. http://dx.doi.org/10.1016/S0360-3016(03)01067-8

Schwartz, G.F., Solin, L.J., Olivotto, I.A., Ernster, V.L., Pressman, P.I., The Consensus Conference Committee. 1999. Consensus conference on the treatment of in situ ductal carcinoma of the breast, April 22-25, 1999. Cancer 88(4), 946-954. http://dx.doi.org/10.1002/(SICI)1097-0142(20000215)88:4<946::AID-CNCR26>3.0.CO;2-5

Siegel, R., Naishadham, D., Jemal, A. Cancer statistics, 2013. 2013. CA Cancer J Clin. 2013;63(1):11–30. http://dx.doi.org/10.3322/caac.21166

Silverstein MJ, Lagios MD, Craig PH, Waisman JR, Lewinsky BS, Colburn WJ, Poller DN. 1996. A prognostic index for ductal carcinoma in situ of the breast. Cancer 77(11), 2267-2274. http://dx.doi.org/10.1002/(SICI)1097-0142(19960601)77:11<2267::AID-CNCR13>3.0.CO;2-V

Silverstein, M.J., Lagios, M.D., Groshen, S., Waisman, J.R., Lewinsky, B.S., Martino, S., Gamagami, P., Colburn, W.J. 1996. The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med 340(19), 1455-1461. http://dx.doi.org/10.1056/NEJM199905133401902

Wang, S.Y., Chu, H., Shamliyan, T., Jalal, H., Kuntz, K.M., Kane, R.L., and Viring, B.A. 2012. Network meta-analysis of margin threshold for women with ductal carcinoma in situ. J Natl J Inst 104, 507-516. http://dx.doi.org/10.1093/jnci/djs142

Welch, H.G., Woloshin, S., and Schwartz, LM. 2008. The sea of uncertainty surrounding ductal carcinoma in situ – The price of screening mammography. J Natl J Inst 100(4), 228-229. http://dx.doi.org/10.1093/jnci/djn013

Yamashita et al. Radiation Oncology 2014, 9:112
http://www.ro-journal.com/content/9/1/112

RADIATION ONCOLOGY

RESEARCH Open Access

Local effect of stereotactic body radiotherapy for primary and metastatic liver tumors in 130 Japanese patients

Hideomi Yamashita[1*], Hiroshi Onishi[2], Yasuo Matsumoto[3], Naoya Murakami[4], Yukinori Matsuo[5], Takuma Nomiya[6], Keiichi Nakagawa[1] and Japanese Radiological Society multi-institutional SBRT study group (JRS-SBRTSG)

Abstract

Background and aims: Stereotactic body radiotherapy (SBRT) is a relatively new treatment for liver tumor. The outcomes of SBRT for liver tumor unfit for ablation and surgical resection were evaluated.

Methods: Liver tumor patients treated with SBRT in seven Japanese institutions were studied retrospectively. Patients given SBRT for liver tumor between 2004 and 2012 were collected. Patients treated with SBRT preceded by trans-arterial chemoembolization (TACE) were eligible. Seventy-nine patients with hepatocellular carcinoma (HCC) and 51 patients with metastatic liver tumor were collected. The median biologically effective dose (BED) ($\alpha/\beta = 10$ Gy) was 96.3 Gy for patients with HCC and 105.6 Gy with metastatic liver tumor.

Results: The median follow-up time was 475.5 days in patients with HCC and 212.5 days with metastatic liver tumor. The 2-year local control rate (LCR) for HCC and metastatic liver tumor was 74.8% ± 6.3% and 64.2 ± 9.5% ($p = 0.44$). The LCR was not different between $BED_{10} \geq 100$ Gy and < 100 Gy ($p = 0.61$). The LCR was significantly different between maximum tumor diameter > 30 mm vs. ≤ 30 mm (64% vs. 85%, $p = 0.040$) in all 130 patients. No grade 3 laboratory toxicities in the acute, sub-acute and chronic phases were observed.

Conclusions: There was no difference in local control after SBRT in the range of median BED_{10} around 100 Gy for between HCC and metastatic liver tumor. SBRT is safe and might be an alternative method to resection and ablation.

Summary: There was no difference in local control after SBRT in the range of median BED_{10} around 100 Gy for between HCC and metastatic liver tumor and SBRT is safe and might be an alternative method to resection and ablation.

Keywords: Hepatocellular carcinoma, Metastatic liver tumor, Stereotactic body radiotherapy, Stereotactic ablative radiotherapy

Introduction

In Japan, an infection rate of the hepatitis C is high, and there are many hepatocellular carcinoma (HCC) cases. The liver is also a common lesion of metastases from most common solid malignancies. According to clinical practice guidelines from Japan, resection, radiofrequency ablation (RFA), and liver transplantation are the available curative options for HCC [1]. Recently, stereotactic body radiotherapy (SBRT) has become a treatment option for patients with liver tumor who are not eligible for surgery, RFA, or liver transplantation. Although HCC doesn't really have bad radiation sensitivity [2], what's happening now is that SBRT for HCC has not been performed very much. One of the reasons is that the role of radiotherapy (RT) for liver tumors has been limited due to the risk of radiation-induced liver disease (RILD) [3]. However, technological advances have made it possible for radiation to be delivered to small liver tumors while reducing the risk of RILD [4]. Resection, RFA, or trance-catheter arterial chemoembolization (TACE) are often performed for HCC and liver metastasis in Japan. However, only 10–20% of HCC patients have a resectable disease [5]. A drawback to RFA is that

* Correspondence: yamachan07291973@yahoo.co.jp
[1]Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Full list of author information is available at the end of the article

some anatomic areas make the procedure difficult to perform [6]. It is only the case with a central lesion of the liver, with direct invasion into the vessels, and/or that an effect of TACE was insufficient to be introduced to SBRT. In patients with centrally located HCC with chronic hepatitis or cirrhosis, major resection is often contraindicated due to insufficient residual liver volume [7]. RFA is therefore often contraindicated for HCC in those areas, which are located in and near the hepatic portal vein or central bile duct [8] and abutting the diaphragm [6]. Additionally, the risk of neoplastic seeding along the needle track after RFA has been reported [9].

SBRT offers an alternative, non-invasive approach to the treatment of liver metastasis. The goal of SBRT is to deliver a high dose to the target, thereby providing better local tumor control, while limiting dose to surrounding healthy tissue, thereby potentially decreasing complication rates. Early applications of SBRT to liver metastases have been promising [10-20]. While these data establish the safety of stereotactic radiation therapy for liver metastases, all SBRT treatments must be performed cautiously given the challenges of organ motion and the low radiation tolerance of the surrounding hepatic parenchyma.

Takeda *et al.* [21] reported that local control rate (LCR) after SBRT for lung metastases from colorectal cancer with a 2-year LCR of 72% was worse than that for primary lung cancer. We hypothesized that the same thing as this might apply to HCC and liver metastasis and, in other words, LCR after SBRT for liver metastases might be worse than that for HCC.

Because there was little number of cases that has performed liver SBRT in every each institution, we wanted to research results and a side effect as a whole in many institutions. The purpose of this study was to retrospectively evaluate the outcomes, mainly concerning local control, of patients treated at various dose levels in many Japanese institutions.

Materials and methods

Patients

This is a retrospective study to review 130 patients with primary or metastatic liver cancers treated at seven institutions extracted from the database of Japanese Radiological Society multi-institutional SBRT study group (JRS-SBRTSG). The investigation period was from May 2004 to November 2012.

The diagnosis of HCC depended mostly on imaging studies, because candidates for SBRT were unfeasible for pathological confirmation. During follow-up of patients with liver disease, nodules ≥1 cm were diagnosed as HCC based on the typical hallmarks (hyper-vascular in the arterial phase with washout in the portal, venous or delayed phases) from imaging studies, which included a combination of contrast-enhanced ultrasonography, 4-phase multi-detector computed tomography (CT), dynamic contrast-enhanced magnetic resonance imaging (MRI), and CT during hepatic arteriography and arterio-portography studies. The diagnosis was established according to a review [22] and clinical practice guidelines [23,24]. The eligibility of SBRT for HCC was a single lesion in principle.

The diagnosis of metastatic liver tumor was confirmed by diagnostic imaging including ultrasound, CT, and/or MRI. The eligibility of SBRT for metastatic liver tumor was without other lesions and in less than four.

Patient and tumor characteristics were shown in Table 1. HCC included 79 cases and the liver metastases included 51 cases. The Child-Pugh score before SBRT for HCC was 84.8% in grade A, 11.4% in grade B, and 1.3% in grade C. Ischemic HCC was 16/79 cases (20%) and plethoric HCC was 55/79 cases (70%). The median alpha-fetoprotein (AFP) (ng/mL) and des-gamma carboxy prothrombin (PIVKA-II) (AU/mL) value before SBRT for evaluable 73 patients with HCC were 12.7 (range; 0.8-8004) and 35 (range; 3.1-16900). The median indocyanine green retention rate at 15 min (ICG15) value before SBRT for evaluable 25 patients with HCC was 21.2% (range; 3–56.2%). This SBRT was the first treatment in 26/79 cases (33%) and was the first treatment about the same lesion as this SBRT in the additional 7 cases. About the primary tumor site of liver metastases, colo-rectum was 58.8%, lung was 9.8%, and stomach was 9.8%. The number of SBRT lesions was from 1 to 4 (solitary was 41/51 cases) for liver metastasis.

Treatment

For treatment planning, abdominal pressure corsets such as body shell or vacuum cushion such as blue back were used, and it was confirmed that tumor motion was <1 cm. Then, the gross tumor volume (GTV) was delineated on the both inspiratory and expiratory planning CT images in the case of respiratory depression method. The breath-holding method was used in 36 cases, gating method in 10 cases, and respiratory depression method in 25 cases about HCC patients. The planning target volume (PTV) was configured considering respiratory movement, a set-up margin, and a sub-clinical margin (Figure 1). SBRT was performed with an X-ray beam linear accelerator of 6 MV. The total dose was delivered depending on judgment each institution. A collapsed cone (CC) convolution, superposition algorithm, or analytical anisotropic algorithm (AAA) was used for dose calculations.

The mode value of total irradiated dose was 48 Gy in 4 fractions (38/79 cases) (from 40 Gy in 4 fractions to 60 Gy in 10 fractions) for HCC and 48 Gy in 4 fractions (12/51 cases) and 52 Gy in 4 fractions (16/51 cases) (from 30 Gy in 3 fractions to 60 Gy in 8 fractions) for metastatic liver tumor. The biologically effective dose

Table 1 Patient and tum or characteristics of SBRT

Liver metastasis	N	%	HCC	N	%
	51	100		79	100
Primary cancer			Stage		
Colon cancer	21	41.2	I	29	36.7
Rectal cancer	9	17.6	II	21	26.6
Lung cancer	5	9.8	III	5	6.3
Gastric cancer	5	9.8	IV	2	2.5
Cervical cancer	3	5.9	Recurrence	11	13.9
Breast cancer	3	5.9	NE	11	13.9
Pancreatic cancer	3	5.9			
Bile duct cancer	1	2.0			
Skin cancer	1	2.0			
Number of SRT			Chilid-Pugh before SBRT		
Single SRT	41	80.4	A	67	84.8
Two places	8	15.7	B	9	11.4
Tree	1	2.0	C	1	1.3
Four	1	2.0	NE	2	2.5
Sex					
Female	17	33.3		19	24
Male	34	66.7		60	75.9
Tumor diameter (mm)					
Range	13-54			6-70	
Median	26			27	
Performance status (ECOG)					
0	32	62.7		34	43.0
1	13	25.5		39	49.4
2	5	9.8		4	5.1
3	1	2.0		1	1.3
Age (years old)					
Range	33-90			38-95	
Median	73			73	
SRT total dose (Gy)					
Range	30-60			40-60	
Median	50			48	
BED-10 (Gy)					
Range	56-134.4			75-106	
Median	105.6			96.3	

Abbreviation: NE not evaluable.

(BED) ($\alpha/\beta = 10$ Gy) was 75–106 Gy (median: 96 Gy) for patients with HCC and 56–134 Gy (median: 106 Gy) with metastatic liver tumor (Table 1). The formula about BED_{10} was used; BED (Gy_{10}) = nd $(1 + d/\alpha/\beta)$. In all 130 cases, CT registration like cone beam CT was performed each treatment.

SBRT was delivered using multiple non-coplanar static beams (using > 7 non-coplanar fields) generated by a linear accelerator or volumetric modulated arc therapy. Daily image guidance, by using either orthogonal X-rays or onboard CT imaging, was used to re-localize the target before treatment delivery.

Trans-catheter arterial chemoembolization (TACE) in 7 HCC patients, FOLFILI regimen (folinic acid, fluorouracil, plus irinotecan) in a metastatic liver tumor patient, or TAXOL® (paclitaxel) in a metastatic liver tumor patient was performed before SBRT. Oral TS-1 was combined concurrently with SBRT in an HCC patient.

Follow up

Patients were seen monthly for 1 year after SBRT and tri-monthly thereafter. Laboratory tests were done at every visit. Treatment responses and intrahepatic recurrences were evaluated with dynamic contrast-enhanced CT or MRI every 3 months with modified Response Evaluation Criteria in Solid Tumors (mRECIST) [25]. Toxicity was evaluated with the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Acute and sub-acute toxicities were defined as adverse events occurring within 3 months and 3–6 months, respectively, after SBRT. Late toxicities related with liver and other toxicities were defined as those occurring after 6–12 months and from 6 months to last follow-up, respectively. Laboratory tests included aspartate aminotransferase, total bilirubin, platelet count, and albumin.

Local recurrence was defined as progressive disease in mRECIST or the new appearance of a lesion within the PTV, and local control was defined as free of local recurrence. Local control was defined as freedom from local progression by mRECIST.

Statistical analysis

Control and survival rates were calculated with Kaplan-Meier analysis. Log-rank testing was used to compare outcomes between the subsets of patients analyzed. Cox proportional hazards regression analysis was used for multivariate analysis. A p-value of <0.05 was considered significant. Data were analyzed with SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA). The points on survival curves by Kaplan Meier are a censored case.

Results

Eligible patients

The median follow-up time was 475.5 days (range; 101–2050 days) in patients with HCC and 212.5 days (range; 26–2713 days) with metastatic liver tumor. SBRT was performed as scheduled and was feasible in all patients. At the last follow-up, 48/79 cases (61%) were survival and 31/79 (39%) were dead for HCC and 42/51

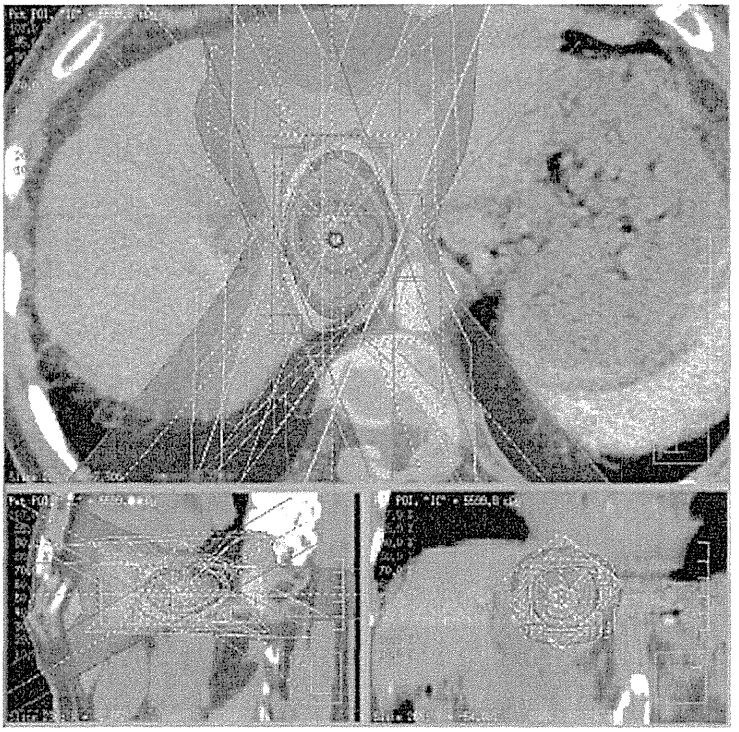

Figure 1 Dose distribution of SBRT for liver tumor. Sky blue line = ITV, purple line = PTV, red area = over 95% dose, green area = 90-95%, blue area = 80-90%, yellow area = 70-80%, purple area = 60-70%, sky blue area = 50-60%, orange area = 30-40%.

cases (82%) were survival and 9/51 cases (18%) were dead for metastatic liver tumors.

Treatment outcomes

Clinical results were shown in Table 2. As to the initial local effect, complete response (CR) and partial response (PR) were 45.6% and 35.4% in SBRT for HCC and 29.4% and 45.1% for metastatic liver tumor, respectively.

Table 2 Clinical results of SBRT

	N	%	N	%
	Liver metastasis		HCC	
First local effect				
CR	15	29.4	36	45.6
PR	23	45.1	28	35.4
MR	2	3.9	0	0
NC	6	11.8	9	11.4
PD	0	0	4	5.1
NE	5	9.8	2	2.5
Local progress				
With	10	19.6	14	17.7
Without	37	72.5	63	79.7
NE	4	7.8	2	2.5

Abbreviation: CR complete response, *PR* partial response, *MR* minor response, *NC* no change, *PD* progress disease, *NE* not evaluable.

The 2-year cumulative LCR for HCC and metastatic liver tumor was 74.8% ± 6.3% (standard error) and 64.2 ± 9.5% ($p = 0.44$) (Figure 2). The LCR was not different between $BED_{10} \geq 100$ Gy (69.0% ± 7.6% at 2 years) vs. < 100 Gy (72.4% ± 7.7%) in all 130 patients ($p = 0.61$) (Figure 3). The LCR was not different between HCC (68.2% ± 11.2%) vs. liver metastasis (68.3% ± 11.2%) in 70 patients with the higher $BED_{10} \geq 100$ Gy ($p = 0.96$). The LCR was not different between $BED_{10} \geq 100$ Gy (68.3% ± 11.2%) vs. < 100 Gy (46.5% ± 16.9%) in 51 patients with liver metastasis (68.2% ± 11.2% vs. 79.2% ± 7.7%, $p = 0.72$) and in 79 patients with HCC ($p = 0.43$). In all 130 patients, the LCR was not different between maximum tumor diameter > 20 mm vs. ≤ 20 mm (70.6% ± 7.6% vs. 83.5% ± 7.6%, $p = 0.28$) and ≥ 40 mm vs. < 40 mm (55.4% ± 17.2% vs. 79.8% ± 5.1%, $p = 0.32$) except for > 30 mm vs. ≤ 30 mm (64.1% ± 9.1% vs. 85.2% ± 5.6%, $p = 0.040$) (Figure 4). The LCR was not different between $BED_{10} \geq 100$ Gy (66.2% ± 33.8%) vs. < 100 Gy (62.3% ± 12.6%) in 41 patients with the bigger tumor diameter > 30 mm ($p = 0.78$). The LCR was not different between older (>70 y.o.) vs. younger (≤70 y.o.) (74.4% ± 6.2% vs. 70.6% ± 8.9%, $p = 0.76$).

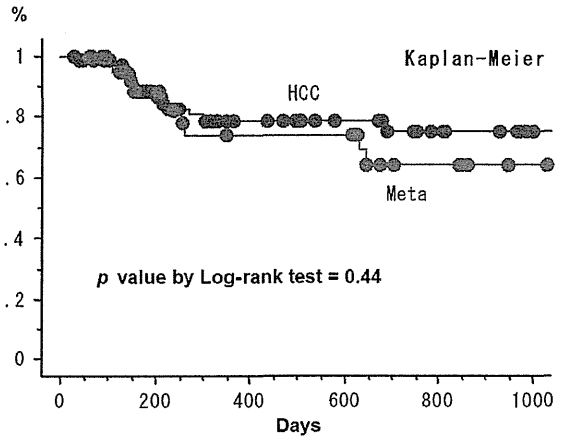

Figure 2 Local control curves between SBRT for hepatic cell carcinoma and metastatic liver tumor. The points on survival curves are a censored case.

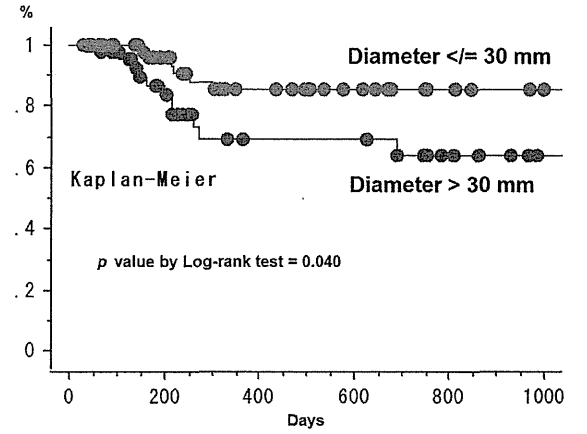

Figure 4 Local control curves between maximum tumor diameter > 30 mm and </=30 mm. The points on survival curves are a censored case.

By multivariate analysis (Cox proportional hazards regression analysis), the maximum tumor diameter > 30 mm vs. ≤ 30 mm (other covariates were $BED_{10} \geq$ 100 Gy vs. <100 Gy of $p = 0.70$, age >70 y.o. vs. ≤ 70 y.o. of $p = 0.73$, HCC vs. metastatic liver tumor of $p = 0.52$) was the only significant factor for LCR ($p = 0.047$, 95% CI = 1.014-7.546).

The scatter diagram between BED_{10} and local control time was shown in Figure 5. There was no correlation between BED_{10} and local control time. We didn't show the fact that the higher BED_{10} was, the longer local control time was.

The 2-year overall survival (OS), cause specific survival (CSS), disease free survival (DFS), and distant metastatic free survival (DMF) were 52.9% ± 7.1%, 69.0% ± 6.9%, 39.9% ± 6.9%, and 76.3% ± 6.6% in 79 patients with HCC, respectively (Figure 6). The number of patients at risk was

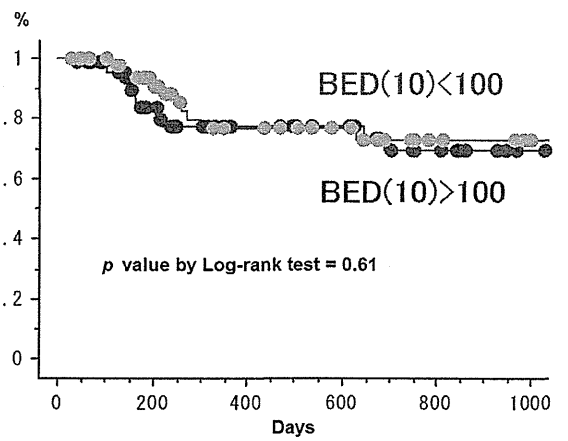

Figure 3 Local control curves between BED (10) > 100 Gy and < 100 Gy. The points on survival curves are a censored case.

43, 21, 9, and 3 at 1-, 2-, 3-, and 4-year in OS, respectively. The 2-year OS was 71.9% ± 9.4% in 51 patients with metastatic liver tumor.

The 2-year cumulative LCR for HCC (n = 79) vs. metastatic liver tumor from colorectal cancer (n = 30) vs. from other cancers (n = 21) was 74.1% ± 6.2% vs. 54.2% ± 11.8% vs. 87.5% ± 11.7% ($p = 0.18$ by comparison among three groups, $p = 0.12$ between colorectal and other cancers, and $p = 0.16$ between HCC and colorectal cancer).

Treatment-related toxicity

All SBRT were completed without toxicity during RT period. There was no Grade 5 toxicity. Nine patients (7%) experienced Grade 2–4 gastrointestinal toxicity. Three patients had Grade 2 gastric inflammations at both 1 Mo (40 Gy in 4 fractions and 60 Gy in 10 fractions) and one gastric ulcer at 27 Mo (60 Gy in 10 fractions). Four had Grade 3 intestinal tract bleedings at 5 Mo (50 Gy in 5 fractions) and 6 Mo (40 Gy in 4 fractions) and transverse colon ulceration at 5 Mo (60 Gy in 10 fractions) and duodenal ulcer at 17 Mo (48 Gy in 4 fractions) without chemotherapy in all 4 cases. One patient had Grade 4 gastro-duodenal artery rupture at 6 Mo after SBRT of 48 Gy in 4 fractions without chemotherapy. One patient complained of chest wall pain after SBRT of 45.2 Gy in 4 fractions combined with TACE.

No significant (≥ grade 3) liver enzyme elevation was observed during treatment. No classic RILD was observed.

Discussion

This is a retrospective study to review 130 patients with primary or metastatic liver cancers treated at 20 institutions extracted from the database of JRS-SBRTSG. The primary aim of the paper is to report outcome in terms

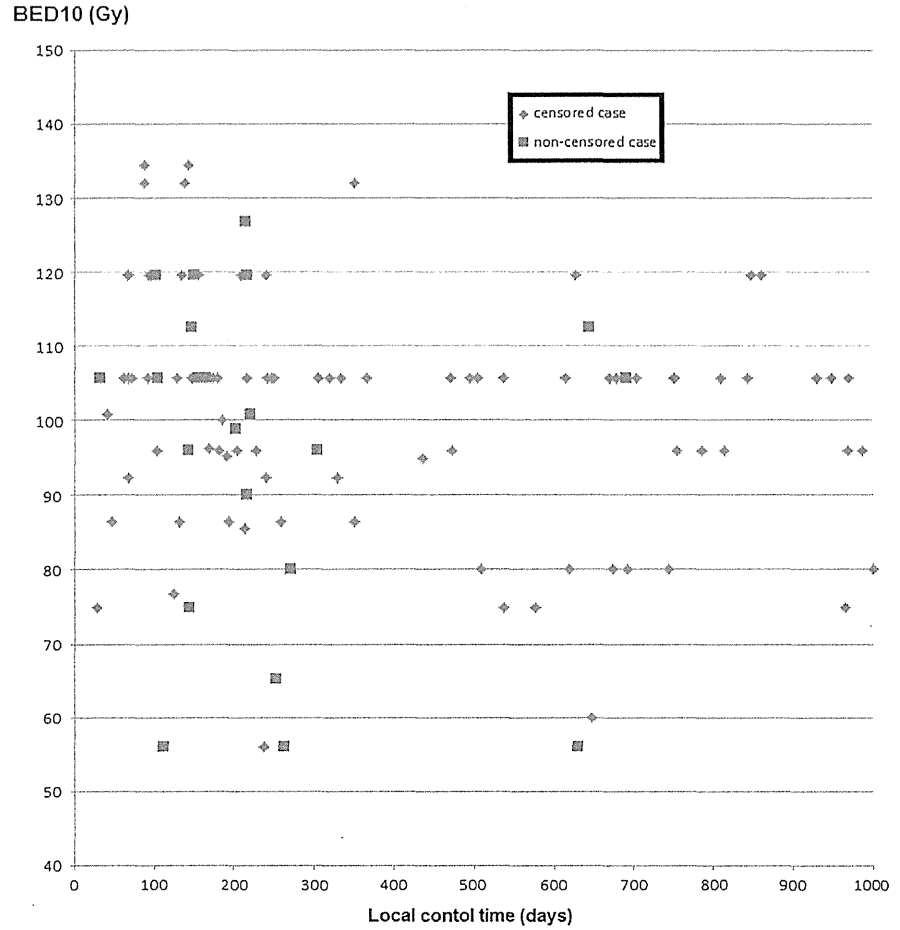

Figure 5 Scatter diagram between BED10 (Gy) and local control time (days).

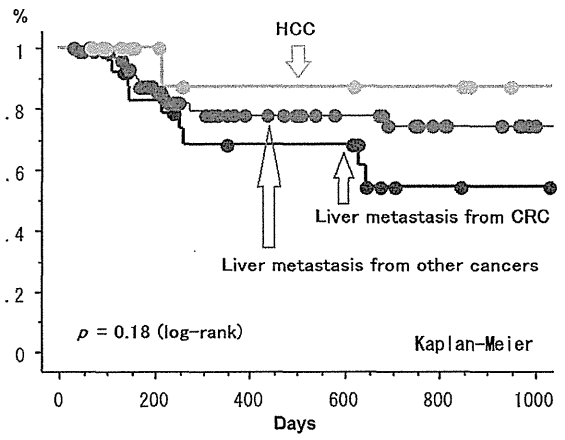

Figure 6 Local control curves among HCC, liver metastases from colorectal cancer, and from other cancers.

of survival, local control, and toxicity. Overall survivals in this study of 53% for HCC (n = 79) and 72% for liver metastases (n = 51) at 2 year after SBRT were almost satisfactory (median follow-up was 16 months), but there were various biases in that the candidates included frail patients contraindicated due to decompensated cirrhosis and older patients with a median age of 73 years. It was the reason why only LCR was performed for the factor analysis in this study.

The local controls after stereotactic body radiotherapy for liver tumor were 65% to 100% in HCC and 56% to 100% in metastatic liver tumor. Results of phase I/II studies and retrospective series of SBRT for HCC patients indicated high local control rates of 90-100% [26-29]. In this study, local recurrence was seen at within 8 months in almost all cases and at 20 to 23 months in some cases. The LCR of HCC in this study was slightly poor and could hardly have been more different from that of metastatic liver tumor. We showed the summary of LC after SBRT for liver tumor in Table 3.