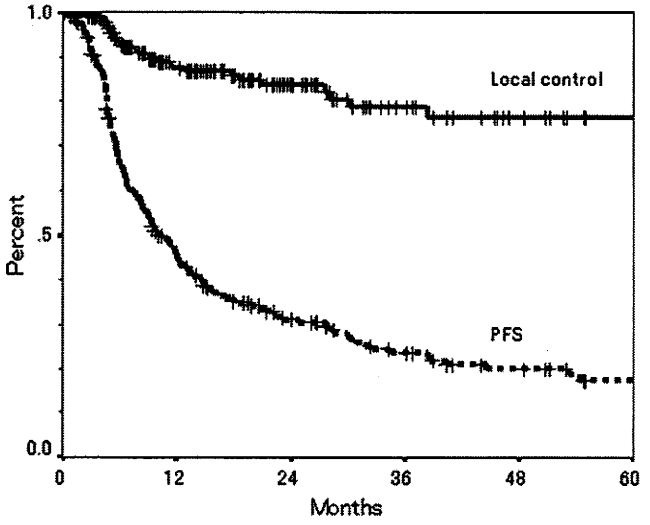

Fig. 1. Local control and progression free survival (PFS) curves for 210 patients with pancreatic cancer who were treated with gross complete resection.

according to the degree of resection in each treatment modality group.

The median follow-up of the surviving 62 patients was 26.3 months (range, 2.7–90.5 months). Overall survival (OS), progression-free survival, metastasis-free rates, and local control rates were calculated actuarially according to the Kaplan-Meier method (11) and were measured starting from the day of initial treatment. Differences between groups were estimated using the chi-square test, Student's *t* test, and the log rank test (12). Multivariate analysis was performed using the Cox regression model (13). A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed using the SPSS software package (version 11.0; SPSS, Inc., Chicago, IL). Late complications were graded in accordance with the National Cancer Institute—Common Terminology Criteria (NCI-CTC) Version 3.0.

RESULTS

At the time of this analysis, 150 patients (70.0%) had disease recurrence (local only in 23 patients; regional lymph nodes only in 7 patients; liver only in 49 patients; peritoneum only in 28 patients; other distant metastases, such as at bone or lung, only in 16 patients; and multiple sites in 43 patients). Among 43 patients with multiple recurrences, 9 patients had a simultaneous local recurrence. Therefore, local recurrence occurred in a total of 31 patients (14.8%). The 2-year actuarial local control rate in all 210 patients after radiotherapy was 83.7% (Fig. 1). Patients who underwent R0 resection had a statistically significantly higher local control than those who underwent R1 resection ($p = 0.0226$), and the 2-year actuarial local control rates in patients who underwent R0 resection and R1 resection were 87.1% and 74.6%, respectively (Table 6). By contrast, other factors, such as CA19-9, the use of chemotherapy, pathological N stage, and IORT dose, did not influence local control (Table 6).

The proportions of patients with locally controlled disease were analyzed with respect to IORT doses, degree of resection, and RT modality (Table 7). In patients treated with R0 resection, the incidence of locally control was highest in patients treated with 25 Gy-IORT + EBRT (96%) in comparison with other subgroups. However, no significant difference in local control was observed in comparison with patients treated with 25 Gy-IORT (93%, $p = 0.6259$). Furthermore, in patients treated with R1 resection, the incidence of local control was highest in patients treated with 25 Gy-IORT + EBRT (90%) compared with that in any other subgroups. Nevertheless, no significant difference in local control was noted between patients treated with 25 Gy-IORT and EBRT and those treated with 25 Gy-IORT alone (69%, $p = 0.2109$).

Table 6. Local control rates and metastasis-free rates according to the degree of resection, CA 19-9 level, chemotherapy use, pathological N stage, and IORT dose

	No. of Patients	2-year LCR (%)	*p* Value	2-year MFR (%)	*p* Value
Degree of resection					
R0	147	87.1	0.0226	44.6	0.0148
R1	63	74.6		25.8	
CA19-9 (U/mL)					
< 1000	160	84.2	0.5217	43.9	0.0030
≥ 1000	38	79.2		21.0	
Chemotherapy use					
Yes	96	88.6	0.2569	47.2	0.0044
No	114	80.5		29	
Pathological N stage					
N0	51	81.9	0.8059	61.9	0.0001
N1	153	85.2		30.2	
IORT dose					
< 25 Gy	64	78.1	0.1225	45.8	0.238
≥ 25 Gy	146	86.4		36.2	

Abbreviations: LCR = local control rate; MFR = metastasis-free rate; CA19-9 = carbohydrate antigen 19-9; R0 = gross complete resection with negative margins; R1 = gross complete resection with positive margins; IORT = intraoperative radiotherapy.

Of the 210 patients, 148 (70.5%) died during the period of this analysis. Of those 148 patients, 134 patients died of pancreatic cancer and the remaining 14 patients died without any sign of clinical recurrence (9 died of intercurrent disease and 5 of unknown cause). The 2-year actuarial progression-free survival rate and the median time to progression for all 210 patients were 31.2% and 10.1 months, respectively (Fig. 1). Table 4 indicates the metastasis-free rates according to the degree of resection, level of CA19-9, use of chemotherapy, and IORT dose. Degree of resection, CA19-9 level, chemotherapy use, and pathological N stage significantly influenced the metastasis-free rates, whereas IORT dose did not influence the metastasis-free rate. Figure 2 indicates the OS curves in all 210 patients. The median survival time and the 2-year actuarial OS rate in all 210 patients were 19.1 months and 42.1%, respectively. Concerning the use of chemotherapy, the 2-year OS rates for patients treated with chemotherapy (48.0%) was significantly higher than for those treated without chemotherapy (34.8%) ($p = 0.0011$, Fig. 3). On univariate analysis, use of chemotherapy, degree of resection, CA 19-9, and pathological N stage had a significant impact on OS and

Table 7. Proportions of patients with locally controlled patients treated with R0 and R1 resection with respect the IORT doses and the combination of EBRT

	No. of Patients	IORT dose			Total
		20 Gy	25 Gy	30 Gy	
R0 resection					
IORT alone	107	16/22 (73%)	39/42 (93%)	38/43 (88%)	93/107 (87%)
IORT + EBRT	40	14/16 (88%)	23/24 (96%)	-	37/40 (93%)
Total	147	30/38 (79%)	100/109 (92%)	38/43 (88%)	130/147 (88%)
R1 resection					
IORT alone	41	11/14 (79%)	11/16 (69%)	9/11 (82%)	31/41 (76%)
IORT + EBRT	22	9/12 (75%)	9/10 (90%)	-	18/22 (82%)
Total	63	20/26 (77%)	20/26 (77%)	9/11 (82%)	49/63 (78%)

Abbreviations: IORT = intraoperative radiotherapy; EBRT = external beam radiotherapy; R0 = gross complete resection with negative margins; R1 = gross complete resection with positive margins.

on multivariate analysis; these four factors also were significant prognostic factors (Tables 8 and 9). Other factors such as tumor size, PS, and radiotherapy modality did not influence OS. At the time of this analysis, 12 of 210 patients (5.7%) had survived for more than 5 years, and all 12 patients had achieved local control.

NCI-CTC Grade 3–4 late gastrointestinal toxicity was observed in 7 patients (3.3%). Four patients experienced Grade 4 toxicity (1 patient with Grade 4 colitis, 2 patients with Grade 4 gastrointestinal bleeding, and 1 patient with Grade 4 ileus). There were no cases of Grade 5 toxicity. Regarding 4 patients who experienced Grade 4 toxicity, 3 of 4 patients (75%) were treated with 30 Gy-IORT

DISCUSSION

The current study indicates that IORT yields an excellent local control rate for resected pancreatic cancer, with a 2-year local control rate of 83.7% in all 210 patients. Several reports have also demonstrated the efficacy of IORT on local control (14–18). Reni *et al.* indicated that for patients with Stage I–II diseases, IORT reduced the local failure rate from 60% to 27% ($p = 0.04$) (14). Alfieri *et al.* noted increased local control with the addition of IORT in resected pancreatic cancer, and they found that local control was 58% in the IORT group vs. 29% in the group that did not receive IORT ($p < 0.01$) (17). Zerbi *et al.* reported that local recurrence was detected in 27.0% of patients treated with surgery and IORT and in 56.4% of patients treated with surgery alone (18). Concerning EBRT, approximately 50% of patients treated with adjuvant EBRT experience local recurrence even after complete resection (4, 7). Considering the low local control rate in patients treated with surgery alone and those treated with adjuvant EBRT, IORT is an attractive treatment modality to achieve local control in patients with resected pancreatic cancer.

Although the efficacy of IORT for local control has been reported, the optimal use of IORT, such as dosing and EBRT combination strategies, remains unclarified. From the previous reports on IORT for pancreatic cancer, doses

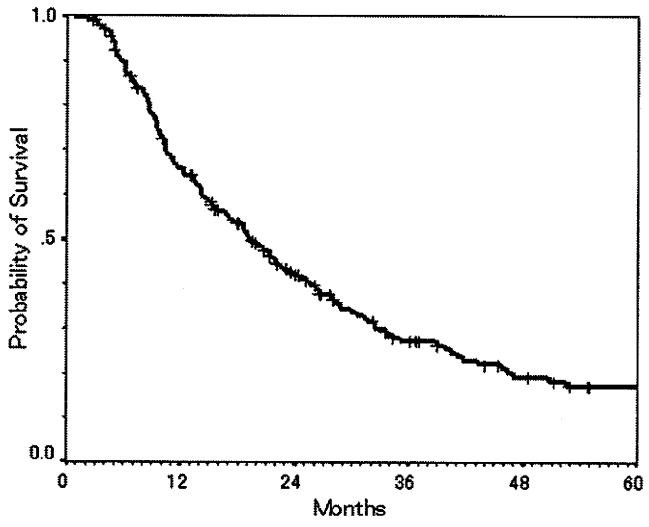

Fig. 2. Actuarial overall survival curves for 210 patients with pancreatic cancer who were treated with gross complete resection.

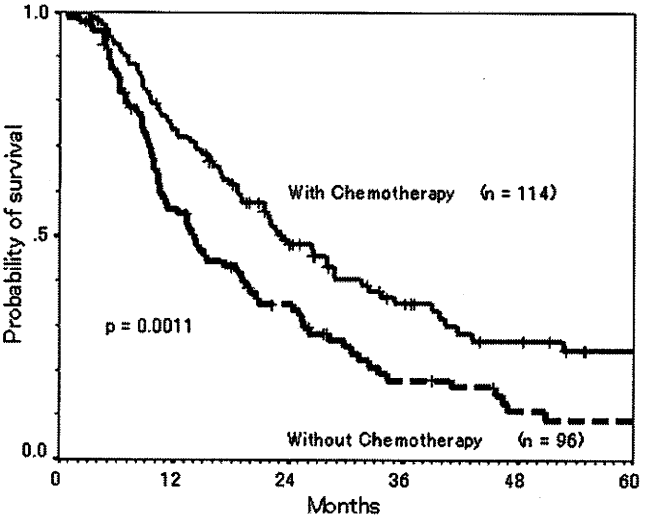

Fig. 3. Actuarial overall survival curves according to chemotherapy administration in patients with pancreatic cancer who were treated with gross complete resection and intraporative radiotherapy. A significant difference was observed between patients who did and did not receive chemotherapy ($p = 0.0011$).

Table 8. Univariate analysis of various potential prognostic factors for overall survival in patients with resected pancreatic cancer treated with IORT

	No. of Patients	Univariate analysis OS, 2- year rate (%)	*p* Value
Degree of resection			
R0	147	50.6	0.0001
R1	63	22.5	
Chemotherapy use			
Yes	114	48.0	0.0011
No	96	34.8	
CA19-9			
< 1000	160	48.2	0.0025
≥ 1000	38	18.9	
Pathological N stage			
N0	51	55.6	0.0038
N1	153	37.8	
Tumor size (cm)			
< 3	92	51.6	0.0550
≥ 3	116	35.0	
RT method			
IORT	148	39.4	0.119
IORT + EBRT	62	48.7	
PS			
0–1	181	43.5	0.2313
2–3	25	33.4	
Gender			
Female	88	41.1	0.5498
Male	122	42.8	
Age (y)			
< 70	143	42.7	0.7161
≥ 70	67	40.9	
Tumor site			
Head/body	197	42.4	0.7593
Tail	13	37.5	
IORT dose (Gy)			
< 25	64	37.1	0.8315
≥ 25	146	44.6	
Pathological T stage			
Tis-2	75	38.9	0.8916
T3–4	134	43.6	

Abbreviations: IORT = intraoperative radiotherapy; R0 = gross complete resection with negative margins; EBRT = external beam radiotherapy; R1 = gross complete resection with positive margins; CA19-9 = carbohydrate antigen; 19-9; PS = performance status.

varied among institutions ranging from 10 to 30 Gy (8, 19), and the optimal dose of EBRT when combined with IORT also has yet to be decided. In the current study, in patients treated with R0 resection, the incidence of locally control in patients treated with 25-Gy IORT (96%) was higher than in other subgroups. Therefore, in patients treated with R0 resection, 25-Gy IORT alone may be sufficient to prevent local recurrence. By contrast, in patients treated with R1 resection, the incidence of locally control in patients treated with 25-Gy IORT + EBRT (90%) was higher than in other subgroups but only 69% in patients treated with 25-Gy IORT alone. These results suggest that in patients treated with R1 resection, 25-Gy IORT alone was insufficient to achieve local control, and 25-Gy IORT + EBRT appears to be most appropriate for these patients. Further studies are required to determine the optimal doses for IORT in this patient population.

Table 9. Multivariate analysis of potential prognostic factors for overall survival in patients with resected pancreatic cancer treated with IORT

Variable	RR (95% CI)	*p* Value
Chemotherapy use (Yes vs. No)	1.795 (1.255–2.569)	0.001
Degree of resection (R0 vs. R1)	0.515 (0.349–0.761)	0.004
CA19-9 (<1000 U/mL vs. ≥ 1000 U/mL)	0.652 (0.430–0.988)	0.044
Pathological N stage (N0 vs. N1)	0.610 (0.388–0.958)	0.032

Abbreviations: IORT = intraoperative radiotherapy; R0 = gross complete resection with negative margins; R1 = gross complete resection with positive margins; RR = relative risk; CI = confidence intervals.

Despite the favorable local control rates in patients treated with IORT, the role of IORT in survival for these patients remains controversial (18–24). Sindelar *et al.* conducted a small randomized trial that compared adjunctive IORT with EBRT in patients with resectable pancreatic cancer and concluded that the survival rate did not differ among patients who received IORT, EBRT, or no EBRT (19). Fossati *et al.* reported that no significant benefit in survival was observed in the IORT group compared with the no-IORT group of 33 patients with resected pancreatic cancer, although the local control rate was significantly better in the IORT group (20). In contrast to these results, however, a survival advantage with IORT was reported by several groups. Ozaki *et al.* (23) suggested that IORT combined with radical resection and extended lymph node dissection may substantially improve survival. Reni *et al.* reported improved median survival with IORT at 18.5 months compared with 13 months in their non-IORT group (14). Therefore, it is important to evaluate possible factors affecting the prognosis of patients who undergo IORT.

Several previous studies have suggested potential prognostic factors associated with OS, such as degree of resection, tumor stage, and tumor size in patients treated with macroscopically gross resection and IORT (24–26). In the current study, chemotherapy use, degree of resection, CA 19-9 level, and pathological N stage were independent prognostic factors for OS. Also, these four factors significantly affected the metastasis-free rate. Therefore, our results indicate that distant metastases remain the major problem affecting survival in these patients. Takamori *et al.* conducted an extended study of radical resection combined with IORT for 41 patients with pancreatic cancer, and local recurrence occurred in only 2 patients (4.9%), but cancer-related death occurred in 32 patients, 18 of whom had liver metastases (16). Furuse *et al.* conducted a study of IORT and EBRT with prolonged 5-FU infusion in patients with locally advanced pancreatic cancer, and the median survival time of patients without metastatic spread in the abdominal cavity was 12.9 months, whereas that of patients with metastatic spread was 5.8 months (27). Several other reports have indicated that the local and distant recurrence rates in these and other studies vary from 12 to 50% and 42 to 94%, respectively, with the use of IORT (14, 17, 28, 29). Therefore, in addition to achieving

local control, preventing distant metastases appears to be necessary for improving the prognosis of these patients.

Our results indicated that IORT combined with chemotherapy confers a survival benefit to pancreatic cancer patients in comparison with IORT alone. The use of chemotherapy also reduced the metastasis-free rate, suggesting that chemotherapy may prevent distant metastasis of these tumors. Recent reports have indicated that adjuvant radiotherapy and chemotherapy improves survival after surgery in comparison with patients with observation (30, 31). Herman *et al.* analyzed 908 patients who were treated with pancreaticoduodenectomy and found that adjuvant concurrent 5-FU–based chemotherapy and radiotherapy significantly improves OS in comparison with patients not receiving chemotherapy and radiotherapy (30). Corsini *et al.* reported the results in 472 patients treated with R0 resection, and OS was better in patients who received adjuvant chemotherapy and radiotherapy than in those not receiving chemotherapy and radiotherapy (31). Regarding drugs for pancreatic cancer, 5-FU, with or without mitomycin-C, has been frequently used for therapy of pancreatic cancer (32, 33). Recently, single-agent gemcitabine was found to be marginally superior in clinical benefit and survival compared with 5-FU, and a single-agent gemcitabine has become the standard first-line agent for the treatment of pancreatic cancer (34). More recent reports have indicated that S-1 and UFT are promising agents for pancreatic cancer (35, 36). Further evaluations of optimal sequencing of radiotherapy and these chemotherapy agents should be performed to maximize treatment outcomes for pancreatic cancer patients.

In the current study, 12 of 210 patients (5.7%) survived for more than 5 years, and all 12 patients had achieved local control. Recent reports have also indicated that achieving local control is associated with improved survival for patients with resected tumors (37–39). Valentini *et al.* indicated that patients achieving local control had significantly more favorable OS (3-year OS: 28.4%) than did patients who did not achieve local control (3-year OS: 11.9%) when treated with IORT (37). These results suggested that although metastasis still remains as the primary challenge for treatment of pancreatic cancer, improvement of local control induced by higher radiotherapy doses may affect the survival of patients who tend to have less disseminated disease. Inasmuch as chemotherapy alone appears to be insufficient for inducing favorable local control (Table 6), IORT represents an important treatment modality for better achievement of this goal.

In the current study, the frequency of severe late toxicity was only 3%, highlighting the safety of IORT treatment. Several other reports have also described the feasibility of IORT for pancreatic cancer (14, 15, 24, 40). Toxicity is different for each tissue type, but doses of approximately 25 Gy are generally well tolerated with IORT (41). In the current study, 3 of 4 patients who experienced Grade 4 toxicity (75%) were treated with 30 Gy-IORT, and 30 Gy-IORT may be associated with higher risk of late complications for these tumors. Therefore, when IORT is used, a dose of 25 Gy appears to be appropriate for these tumors. Further studies are required to determine the optimal timing and dose of EBRT when combined with IORT.

In conclusion, our results indicate that IORT yields an excellent local control rate for resected pancreatic cancer, with few severe late toxicities. Our results also suggest that IORT combined with chemotherapy confers a survival benefit in comparison with IORT alone. Inasmuch as IORT can result in favorable local control and the addition of chemotherapy increases the OS rate, IORT combined with chemotherapy appears to be a promising strategy for patients treated with gross complete resection. However, this study is a retrospective study with various treatment modalities, and further prospective studies are required to confirm our results.

REFERENCES

1. Jemal A, Siegel R, Ward E, *et al.* Cancer statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
2. Gudjonsson B. Cancer of the pancreas: 50 years of surgery. *Cancer* 1987;60:2284–2303.
3. Tepper J, Nardi G, Sutt H. Carcinoma of the pancreas: Review of MGH experience from 1963 to 1973: Analysis of surgical failure and implications for radiation therapy. *Cancer* 1976; 37:1519–1524.
4. Griffin JF, Smalley SR, Jewell W, *et al.* Patterns of failure after curative resection of pancreatic carcinoma. *Cancer* 1990;66:56–61.
5. Bosset JF, Pavy JJ, Gillet M, *et al.* Conventional external irradiation alone as adjuvant treatment in resectable pancreatic cancer: Results of a prospective study. *Radiother Oncol* 1992;24: 191–194.
6. Rich TA, Evans DB, Curley SA, *et al.* Adjuvant radiotherapy and chemotherapy for biliary and pancreatic cancer. *Ann Oncol* 1994;5(Suppl. 3):75–80.
7. Evans DB, Abbruzzese JL, Rich TA. Cancer of the pancreas. In: DeVita VT Jr., Hellmann S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 5th ed. Philadelphia: Lippincott; 1997. p. 1054–1087.
8. Ruano-Ravina A, Almazán Ortega R, Guedea F. Intraoperative radiotherapy in pancreatic cancer: A systematic review. *Radiother Oncol* 2008;87:318–325.
9. Ogawa K, Ito Y, Karasawa K, *et al.* Patterns of radiotherapy practice for pancreatic cancer in Japan: Results of the Japanese Radiation Oncology Study Group (JROSG) Survey. *Int J Radiat Oncol Biol Phys.* In press.
10. Sobin LH, Wittelind C. TNM classification of malignant tumours. 6th ed. New York: John Wiley; 2002.
11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
12. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163–170.
13. Cox DR. Regression models and life tables. *J R Stat Soc* 1972; 34:187–220.
14. Reni M, Panucci MG, Ferreri AJ, *et al.* Effect on local control and survival of electron beam intraoperative irradiation for

resectable pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2001;50:651–658.
15. O'Connor JK, Sause WT, Hazard LJ, *et al.* Survival after attempted surgical resection and intraoperative radiation therapy for pancreatic and periampullary adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2005;63:1060–1066.
16. Takamori H, Hiraoka T, Kanemitsu K, *et al.* Long-term outcomes of extended radical resection combined with intraoperative radiation therapy for pancreatic cancer. *J Hepatobiliary Pancreat Surg* 2008;15:603–607.
17. Alfieri S, Morganti AG, Di Giorgio A, *et al.* Improved survival and local control after intraoperative radiation therapy and postoperative radiotherapy: A multivariate analysis of 46 patients undergoing surgery for pancreatic head cancer. *Arch Surg* 2001;136:343–347.
18. Zerbi A, Fossati V, Parolini D, *et al.* Intraoperative radiation therapy adjuvant to resection in the treatment of pancreatic cancer. *Cancer* 1994;73:2930–2935.
19. Sindelar WF. Clinical experience with regional pancreatectomy for adenocarcinoma of the pancreas. *Arch Surg* 1989;124:127–132.
20. Fossati V, Cattaneo GM, Zerbi A, *et al.* The role of intraoperative therapy by electron beam and combination of adjuvant chemotherapy and external radiotherapy in carcinoma of the pancreas. *Tumori* 1995;81:23–31.
21. Kokubo M, Nishimura Y, Shibamoto Y, *et al.* Analysis of the clinical benefit of intraoperative radiotherapy in patients undergoing macroscopically curative resection for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2000;48:1081–1087.
22. Messick C, Hardacre JM, McGee MF, *et al.* Early experience with intraoperative radiotherapy in patients with resected pancreatic adenocarcinoma. *Am J Surg* 2008;195:308–311.
23. Ozaki H, Kinoshita T, Kosuge T, *et al.* Effectiveness of multimodality treatment for resectable pancreatic cancer. *Int J Pancreatol* 1990;7:195–200.
24. Hosotani R, Kogire M, Arii S, *et al.* Results of pancreatectomy with radiation therapy for pancreatic cancer. *Hepatogastroenterology* 1997;44:1528–1535.
25. Okamoto A, Tsuruta K, Karasawa K, *et al.* Resection versus palliation: Treatment of stage III and IVA carcinomas of the pancreas employing intraoperative radiation. *World J Surg* 2003;27:599–605.
26. Nishimura Y, Hosotani R, Shibamoto Y, *et al.* External and intraoperative radiotherapy for resectable and unresectable pancreatic cancer: Analysis of survival rates and complications. *Int J Radiat Oncol Biol Phys* 1997;39:39–49.
27. Furuse J, Kinoshita T, Kawashima M, *et al.* Intraoperative and conformal external-beam radiation therapy with protracted 5-fluorouracil infusion in patients with locally advanced pancreatic carcinoma. *Cancer* 2003;97:1346–1352.
28. Pisters PW, Wolff RA, Janjan NA, *et al.* Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: Toxicities, histologic response rates, and event-free outcome. *J Clin Oncol* 2002;20:2537–2544.
29. Schwarz RE, Smith DD, Keny H, *et al.* Impact of intraoperative radiation on postoperative and disease-specific outcome after pancreatoduodenectomy for adenocarcinoma: A propensity score analysis. *Am J Clin Oncol* 2003;26:16–21.
30. Herman JM, Swartz MJ, Hsu CC, *et al.* Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol* 2008;26:3503–3510.
31. Corsini MM, Miller RC, Haddock MG, *et al.* Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: The Mayo Clinic experience (1975–2005). *J Clin Oncol* 2008;26:3511–3516.
32. Moertel CG, Reitemeier RJ, Hahn RG. Mitomycin C therapy in advanced gastrointestinal cancer. *JAMA* 1968;204:1045–1048.
33. Buroker T, Kim PN, Groppe C, *et al.* 5 FU infusion with mitomycin-C vs. 5 FU infusion with methyl-CCNU in the treatment of advanced upper gastrointestinal cancer: A Southwest Oncology Group Study. *Cancer* 1979;44:1215–1221.
34. Burris HA 3rd, Moore MJ, Andersen J, *et al.* Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol* 1997;15:2403–2413.
35. Ikeda M, Okusaka T, Ito Y, *et al.* A phase I trial of S-1 with concurrent radiotherapy for locally advanced pancreatic cancer. *Br J Cancer* 2007;96:1650–1655.
36. Childs HA 3rd, Spencer SA, Raben D, *et al.* A phase I study of combined UFT plus leucovorin and radiotherapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2000;47:939–944.
37. Valentini V, Morganti AG, Macchia G, *et al.* Intraoperative radiation therapy in resected pancreatic carcinoma: Long-term analysis. *Int J Radiat Oncol Biol Phys* 2008;70:1094–1099.
38. Stessin AM, Meyer JE, Sherr DL. Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: An analysis of data from the surveillance, epidemiology, and end results (SEER) registry. *Int J Radiat Oncol Biol Phys* 2008;72:1128–1133.
39. Valentini V, Calvo F, Reni M, *et al.* Intra-operative radiotherapy (IORT) in pancreatic cancer: Joint analysis of the ISIORT-Europe experience. *Radiother Oncol* 2009;91:54–59.
40. Tepper JE, Noyes D, Krall JM, *et al.* Intraoperative radiation therapy of pancreatic carcinoma: A report of RTOG-8505. Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1991;21:1145–1149.
41. Sindelar WF, Kinsella TJ. Normal tissue tolerance to intraoperative radiotherapy. *Surg Oncol Clin North Am* 2003;12:925–942.

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High-dose-rate Intracavitary Brachytherapy Combined with External Beam Radiotherapy for Stage IIIb Adenocarcinoma of the Uterine Cervix in Japan: A Multi-Institutional Study of Japanese Society of Therapeutic Radiology and Oncology 2006–2007 (Study of JASTRO 2006–2007)

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Objective: The current study was a retrospective questionnaire survey of stage IIIb adenocarcinoma of the uterine cervix treated with high-dose-rate intracavitary brachytherapy combined with external beam radiation therapy in Japan aimed to investigate the optimal dose on the basis of the biological effective dose and prognostic factors.

Methods: Between 1990 and 2000, 61 patients with stage IIIb adenocarcinoma of the uterine cervix underwent high-dose-rate intracavitary brachytherapy combined with external beam radiation therapy in 19 major hospitals in Japan. This retrospective questionnaire survey was performed by mail including survey charts to be fulfilled by radiation oncologists in these 19 major hospital. Fifty had only adenocarcinoma components and 11 had adenosquamous cell carcinoma components. All patients were treated with high-dose-rate intracavitary brachytherapy combined with external beam radiation therapy. Total biological effective dose ($T\text{-}BED_{10}$) was calculated from the sum of the biological effective doses of the external beam radiation therapy and the intracavitary brachytherapy. Thirty-two patients underwent chemotherapy.

Results: The 5-year overall survival rate of all patients was 20.2%. Stratified by total biological effective dose, the 5-year overall survival rate was 0% for $T\text{-}BED_{10}$ <75 Gy, 24.7% for $T\text{-}BED_{10}$ between 75 and 100 Gy and 0% for $T\text{-}BED_{10}$ >110 Gy ($P = 0.15$). Stratified by histopathology, the 5-year overall survival rate was 22.1% for adenocarcinoma and 13.6% for adenosquamous cell carcinoma ($P = 0.43$). Stratified by chemotherapy, the 5-year overall survival rate was 20.3% in patients who received chemotherapy and 20.4% in patients who did not receive chemotherapy ($P = 0.96$).

Conclusions: The 5-year overall survival rate of stage IIIb adenocarcinoma of the uterine cervix in this retrospective questionnaire survey was 20.2%. The optimal T-BED_{10} and evident prognostic factors were not clear from this questionnaire survey.

Key words: high-dose-rate intracavitary brachytherapy – adenocarcinoma of the uterine cervix – multi-institutional study

INTRODUCTION

Prognosis of stage IIIb adenocarcinoma of the uterine cervix has been reported to be much worse than that of squamous cell carcinoma of the same stage. The 5-year overall survival (OS) rates of stage IIIb adenocarcinoma of the uterine cervix treated with high-dose-rate intracavitary brachytherapy (HDR-ICBT) combined with external beam radiotherapy (EBRT) have been reported to be 0–51.0% (1–3), whereas the survival rates for stage IIIb squamous cell carcinoma of the uterine cervix have been reported to be 47.1– 55.2% (4–6). HDR-ICBT combined with EBRT for stage IIIb adenocarcinoma of the uterine cervix is the community standard treatment in Japan. In the US and some European countries, low-dose rate intracavitary brachytherapy (LDR-ICBT) combined with EBRT is often performed. Eifel et al. (7) and Grigsby et al. (8) have reported that the treatment outcomes of adenocarcinoma of the uterine cervix were almost the same as those of the squamous cell carcinoma using LDR-ICBT. However, these results were from Ib to IIb stage uterine cervical carcinomas. Grigsby et al. (8) pointed out that the 5-year disease-free survival rate after treatment with LDR-ICBT of stage III adenocarcinoma of the uterine cervix (25%) was worse than that of the squamous cell carcinoma (59.1%) ($P = 0.007$).

The optimal radiation dose in this situation has not been established, but in practice the same dose as is given for squamous cell carcinoma, 67–86 Gy_{10},with Gy_{10} the biological effective dose if α/β is 10 (6). Although a recent preliminary study has suggested that a higher biological effective dose (BED) might improve prognosis (3), no large studies have been performed to evaluate this issue. The prognostic factors other than the total dose also have not been defined. Therefore, the purpose of the current retrospective questionnaire survey was to investigate the optimal dose on the basis of the BED and to investigate prognostic factors for stage IIIb adenocarcinoma of the uterine cervix treated with HDR-ICBT combined with EBRT.

PATIENTS AND METHODS

Between 1990 and 2000, 61 patients with stage IIIb adenocarcinoma of the uterine cervix were treated with HDR-ICBT combined with EBRT in 19 Japanese university hospitals and cancer centers. Surveys of the charts were completed by radiation oncologists who fulfilled the JASTRO institutional criteria and who responded 'yes' to the pre-questionnaire survey of willingness to engage in this retrospective questionnaire study. The questionnaires were mailed to 19 Japanese university hospitals and cancer centers in 2007. Patient characteristics are listed in Table 1. The median age was 61.5 years with a range of 30–86 years. Fifty patients had only adenocarcinoma components and 11 had adenosquamous cell carcinoma components. The median tumor diameter was 6.0 cm with a range of 2–15 cm. Thirteen of the 61 patients had vaginal invasion. All patients were staged by physical and pelvic examinations, and according to the Japanese standards of pretreatment investigation were examined by computed tomography in order to rule out patients with distant metastases. All patients were then treated with HDR-ICBT combined with EBRT.

Treatment characteristics are listed in Table 2. HDR-ICBT was performed once a week in 55 patients and twice a week in 6 patients. The median dose per fraction was 6 Gy to point A (range: 5–8 Gy). The median total fraction delivery times was five times (range: one to six times). As for the applicator, 58 patients were treated with tandem plus ovoid applicators and 2 patients were inserted by tandem plus cylinder applicators; only 1 patient was inserted by only the tandem applicator. The total dose of HDR-ICBT to point A was 6.0–30 Gy and the total dose of EBRT midway between the isocenter and the lateral field was 40–59.4 Gy. In the current study, the total BED was calculated as follows: total BED (T-BED_{10}) = BED of EBRT (E-BED_{10}) + BED of HDR-ICBT (A-BED_{10}). The median E-BED_{10} was 60 Gy (range: 48–70.1 Gy), the median A-BED_{10} was 31 Gy (range: 9.6–52.5 Gy) and the median T-BED_{10} was 106.3 Gy (range: 66.9–115.2 Gy). The median overall treatment time (OTT) was 53 days (range: 37–153 days).

Table 1. Patient and tumor characteristics

Age, median (range)	61.5 years (30–86 years)
Maximum tumor diameter (cm), median (range)	6.0 (2.0–15.0)
Histopathology (*n*)	
Adenocarcinoma	50
Adenosquamous cell carcinoma	11
Vaginal invasion (*n*)	13

Table 2. Treatment characteristics

Treatment types (*n*)	
EBRT	61
HDR-ICBT	61
Chemotherapy	
None	29
Any	32
Biological effective dose (BED_{10}) (Gy), median dose (range)	
E-BED_{10}	60.0 (48.0–70.1)
A-BED_{10}	31.0 (9.6–52.5)
T-BED^{a}_{10}	106.3 (66.9–115.2)

EBRT, external radiotherapy; HDR-ICBT, high-dose-rate intracavitary brachytherapy; E-BED, external beam radiation therapy; T-BED, total biological effective dose; A-BED_{10}, BED of HDR-ICBT.
[a]T-BED_{10} = (E-BED_{10}) + (A-BED_{10}).

As is shown in Table 2, 32 patients underwent chemotherapy. Chemotherapy regimens were as follows: 23 underwent treatment with platinum drugs, 3 received CPT-11 and 6 received other chemotherapy. In total, 20 of the 32 patients underwent concurrent chemotherapy, and all of those patients received platinum chemotherapy. After the treatment, all patients were followed by physical and pelvic examinations and computed tomography or magnetic resonance imaging.

For statistical analysis, survival curves were constructed by the Kaplan–Meier method and log-rank test was performed to compare between total dose and clinicopathologic valuables using Dr. SPSS II for Windows (SPSS Inc., USA). Statistical significance was assumed for a two-tailed P value <0.05.

RESULTS

Of the 61 patients, 41 patients relapsed. As for the first site of failure, 20 relapsed in the field, 14 relapsed out of field and 7 relapsed both in field and out of field.

The 5-year OS rate of all patients was 20.2% (Fig. 1), the 5-year relapse-free survival (RFS) rate was 13.4% (Fig. 1) and the 5-year local control rate (LC) was 36.0% (Fig. 2). As shown in Fig. 3, stratified by T-BED_{10}, the 5-year OS was 0% for T-BED_{10} <75 Gy ($n = 2$), 24.7% for 110 Gy ≥ T-BED10 ≥ 75 Gy ($n = 50$) and 0% for T-BED_{10} >110 Gy ($n = 9$) ($P = 0.15$). Stratified by histopathology, the 5-year OS was 22.1% for adenocarcinoma and 13.6% for adenosquamous cell carcinoma ($P = 0.43$). The 5-year OS and 5-year LC were not significantly correlated with the E-BED_{10} or A-BED_{10}. Stratified by age, the 5-year OS was 12.0% when the patient's age was <60 years and 31.0% when the patient's age was ≥60 years ($P = 0.175$). Stratified by PS, the 5-year OS was 17.2% when PS was 0 or 1 and was 33.3% when PS was 2 or 3 ($P = 0.366$).

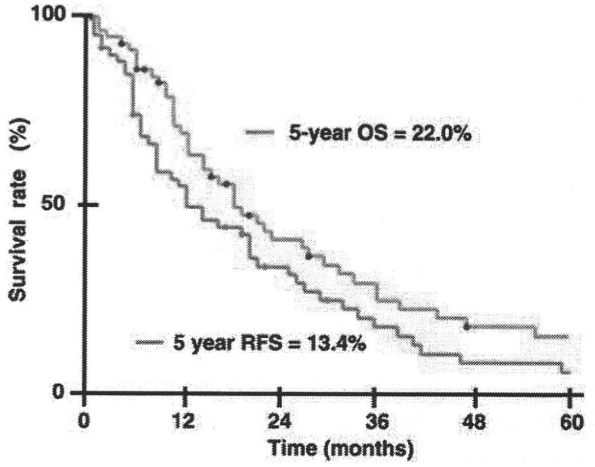

Figure 1. Overall survival (OS) and relapse-free survival curves (RFS) of all patients. The 5-year OS rate was 20.2%. The 5-year RFS rate was 13.4%.

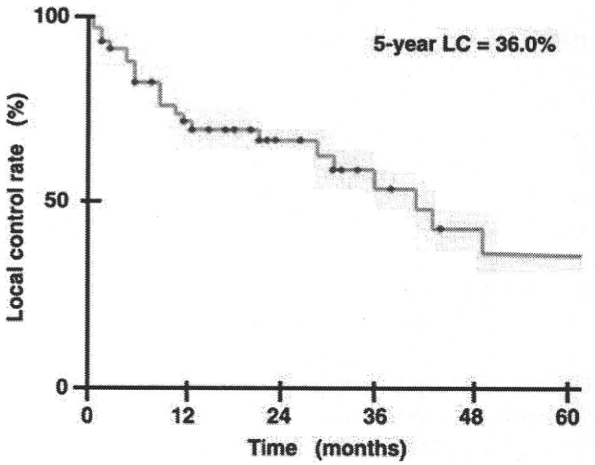

Figure 2. Local control (LC) curve of all patients. The 5-year LC rate was 36.0%.

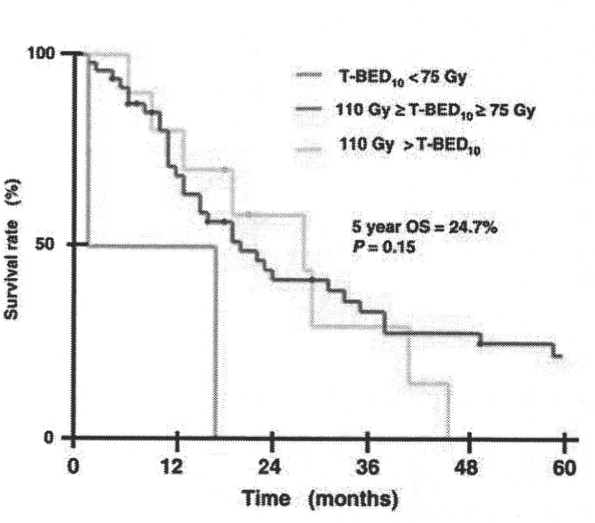

Figure 3. OSl curves stratified by total biological effective dose (T-$BED)_{10}$.

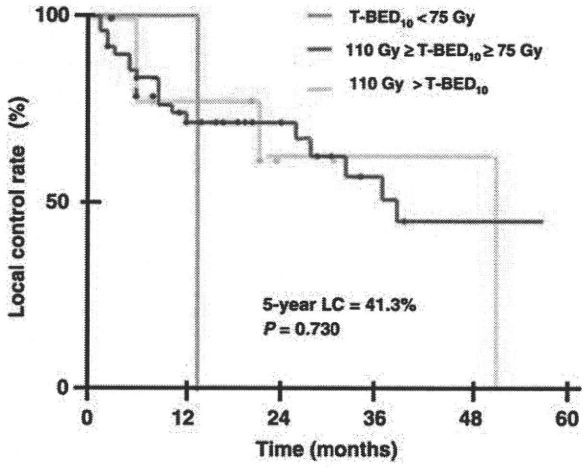

Figure 4. LC curves stratified by Tl-BED_{10}.

Stratified by tumor size, the 5-year OS was 22.2% when the maximum tumor size was <7 cm and 20.0% when the maximum tumor size was ≥7 cm ($P = 0.763$). Stratified by vaginal invasion, the 5-year OS was 50.0% when the lower one-third of the vagina had been invaded: 15.6% when the upper two-thirds of the vagina had been invaded and 19.8% when the vagina was not involved ($P = 0.745$). Stratified by OTT, the 5-year OS was 22.9% when OTT was ≤56 days and 17.8% when it was >56 days ($P = 0.43$). Stratified by chemotherapy, the 5-year OS was 20.3% among those who had undergone chemotherapy and 20.4% among those who had not ($P = 0.96$). Furthermore, the 5-year OS was 15.8% among those who had undergone concurrent chemotherapy and 23.4% among those who had not ($P = 0.566$). As for LC rate stratified by T-BED_{10}, the 5-year LC was 0% for T-BED_{10} <75 Gy, 41.3% for 110 Gy ≥ T-BED_{10} ≥ 75 Gy, and 0% for T-BED_{10} >110 Gy ($P = 0.730$) (Fig. 4).

Eight patients (13.1%) had late morbidity of Grade 2 or greater. Grade 2 late morbidity involved chronic proctitis (rectal bleeding), Grade 3 was characterized by uteric stenosis and recto-vaginal fistula, and Grade 4 involved severe ureter stenosis requiring surgery.

DISCUSSION

The 5-year OS of stage IIIb squamous cell carcinoma of the uterine cervix treated with HDR-ICBT combined with EBRT has been reported to be 47.2–55.2% in Japan (4–6). In the current study, the 5-year OS of stage IIIb adenocarcinoma of the uterine cervix was 20.2% and the 5-year RFS of stage IIIb adenocarcinoma of the uterine cervix was 13.4%, indicating that the prognosis of stage IIIb adenocarcinoma of the uterine cervix is much worse than that of the squamous cell carcinoma of the same stage.

The optimal dose of HDR-ICBT combined with EBRT for stage IIIb adenocarcinoma of the uterine cervix has not been established in a prospective manner. In Japan, 30 years' experience with the use of HDR-ICBT with EBRT for locally advanced uterine cervical carcinoma suggests that 67–86 Gy_{10} is acceptable dose, and this is recognized as the community standard dose (6). Radiation oncologists in the USA have many years of experience using LDR-ICBT with external beam radiotherapy for locally advanced uterine cervical carcinoma, and have calculated the optimal dose of HDR-ICBT from that of LDR-ICBT without performing clinical trials. The American Brachytherapy Society recommends HDR-ICBT dose of 100–108 Gy_{10} for locally advanced uterine cervical carcinoma (9), much higher dose than that generally used in Japan. In both the USA and Japan, the above-mentioned recommendations for the HDR-ICBT dose have been based on locally advanced squamous cell carcinoma rather than adenocarcinoma. Accordingly, the optimal dose of HDR-ICBT combined with EBRT for stage IIIb adenocarcinoma has not been established from any clinical studies.

Recently, a preliminary study of stage IIIb adenocarcinoma of the uterine cervix treated with HDR-ICBT combined with EBRT in Japan suggested that higher T-BED was associated with better prognosis (3). In contrast, in the current study, 5-year OS was 0% for T-BED_{10} >110 Gy (high dose), 24.7% for 110 ≥ T-BED_{10} ≥ 75 (intermediate dose) and 0% for T-BED_{10} <75 (low dose) ($P = 0.15$) (Fig. 3). Furthermore, the 5-year LC was 0% for T-BED_{10} <75 Gy, 41.3% for 110 Gy ≥ T-BED_{10} ≥ 75 Gy and 0% for T-BED_{10} >110 Gy ($P = 0.730$) (Fig. 4). These results suggest that higher total dose does not improve LC or OS of stage IIIb adenocarcinoma of the uterine cervix, although considering that this study is retrospective questionnaire survey.

Modern standard treatment of locally advanced uterine cervical carcinoma comprises concurrent chemoradiotherapy. However, the current study revealed no survival benefit of chemotherapy. Similarly, the RTOG phase III study suggested that the treatment results of stages III and IV uterine cervical carcinoma treated with radiation therapy alone and concurrent chemoradiotherapy were the same by a sub-set analysis (10). This analysis suggests that stage III or IV tumors may require new chemotherapeutic regimens. Vrdoljak et al. (11) reported that concurrent chemoradiotherapy for locally advanced uterine cervical carcinomas including adenocarcinomas using cisplatin and ifosfamide followed by consolidation chemotherapy might be promising. Zarba et al. (12) also reported that concurrent chemoradiotherapy using cisplatin and gemcitabine was efficacious and well tolerated.

In the current study, the extent of vaginal invasion also did not impact the prognosis of stage IIIb adenocarcinoma of the uterine cervix. This suggests that biological behavior has much more influence on the prognosis than the insertion technique of applicators in stage IIIb adenocarcinoma of the uterine cervix. Recently, Niibe et al. (13) reported that concomitant positive expression of HER2 and HIF-1α in locally advanced uterine cervical carcinoma including adenocarcinoma achieved 20-month OS rate of 37.5%, whereas concomitant negative

expression of HER2 and HIF-1α achieved 20-month OS rate of 100% ($P = 0.0032$). This suggests that further studies of the biological behavior of stage IIIb adenocarcinoma and the successful production of molecular-targeted drugs are required.

Other factors, such as histopathology and OTT, had no significant difference in prognosis. As for late morbidity, only eight patients experienced Grade 2 or greater morbidity (13.1%). This is considered acceptable.

In conclusion, the prognosis of stage IIIb adenocarcinoma of the uterine cervix was poor. Higher radiation doses prescribed to adenocarcinoma of the uterine cervix were not correlated with better prognosis in this retrospective questionnaire survey. A prospective study should be conducted in order to evaluate the precise significance of higher radiation doses prescribed to patients with adenocarcinoma of the uterine cervix.

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Conflict of interest statement

None declared.

References

1. Toita T, Takizawa Y, Sueyama H, Sueyama H, Kushi A, Kakihana Y, et al. Radical radiotherapy for adenocarcinoma of the uterine cervix. *Strahlenther Onkol* 1994;170:277–80.
2. Suzuki Y, Nakano T, Arai T, Morita S, Tsujii H, Oka K. Progesterone receptor is a favorable prognostic factor of radiation therapy for adenocarcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 2000;47:1229–34.
3. Niibe Y, Hayakawa K, Kanai T, Tsunoda S, Arai M, Jobo T, et al. Optimal dose for stage IIIB adenocarcinoma of the uterine cervix on the basis of biological effective dose. *Eur J Gynaecol Oncol* 2006;27:47–9.
4. Toita T, Sakumoto K, Higashi M, Ogawa K, Kakinohana Y, Shinzato S, et al. Therapeutic value of neoadjuvant intra-arterial chemotherapy (cisplatin) and irradiation for locally advanced uterine cervical cancer. *Gynecol Oncol* 1997;65:421–4.
5. Hareyama M, Sakata K, Ouchi A, Shirato H, Nishioka T, Nishio M, et al. High-dose rate versus low-dose rate intracavitary therapy for carcinoma of the uterine cervix: a randomized study. *Cancer* 2002;94:117–24.
6. Nakano T, Kato S, Ohono T, Tsujii H, Sato S, Fukihisa K, et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. *Cancer* 2005;103:92–101.
7. Eifel PJ, Bruke TW, Morris M, Smith TL. Adenocarcinoma as an independent risk factor disease recurrence in patients with stage IB cervical carcinoma. *Gynecol Oncol* 1995;59:38–44.
8. Grigsby PW, Perez CA, Kuske RR, Camel HM, Kao MS, Galakatos AE, et al. Adenocarcinoma of the uterine cervix: lack of evidence for a poor prognosis. *Radiother Oncol* 1998;12:289–96.
9. Nag S, Erickson B, Thomadsen B, Orton C, Demanes JD, Petereit D. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;48:201–11.
10. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Eng J Med* 1999;340:1137–43.
11. Vrdoljak E, Omrcen T, Novakovic ZS, Jelavic TB, Prskalo T, Hrepic D, et al. Concomitant chemobrachyradiotherapy with ifosfamide and cisplatin followed by consolidation chemotherapy for women locally advanced carcinoma of the uterine cervix—final results of a prospective phase II-study. *Gynecol Oncol* 2006;103:494–9.
12. Zarba JJ, Jaremtchuk AV, Gonzalez Jazey P, Keropian M, Castagnino R, Mina C, et al. A phase I-II study of weekly cisplatin and gemcitabine with concurrent radiotherapy in locally advanced cervical carcinoma. *Ann Oncol* 2003;14:1285–90.
13. Niibe Y, Watanabe J, Tsunoda S, Arai M, Arai T, Kawaguchi M, et al. Concomitant expression of HER2 nad HIF-1α is a poor prognostic factor in uterine cervical carcinoma treated with concurrent chemoradiotherapy: prospective analysis (KGROG0501). *Eur J Gynaecol Oncol*, in press.

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CLINICAL INVESTIGATION

RADICAL EXTERNAL BEAM RADIOTHERAPY FOR CLINICALLY LOCALIZED PROSTATE CANCER IN JAPAN: CHANGING TRENDS IN THE PATTERNS OF CARE PROCESS SURVEY

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Purpose: To delineate changing trends in radical external beam radiotherapy (EBRT) for prostate cancer in Japan.
Methods and Materials: Data from 841 patients with clinically localized prostate cancer treated with EBRT in the Japanese Patterns of Care Study (PCS) from 1996 to 2005 were analyzed.
Results: Significant increases in the proportions of patients with stage T1 to T2 disease and decrease in prostate-specific antigen values were observed. Also, there were significant increases in the percentages of patients treated with radiotherapy by their own choice. Median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing to 70 Gy from 2003 to 2005. Moreover, conformal therapy was more frequently used from 2003 to 2005 (84.9%) than from 1996 to 1998 (49.1%) and from 1999 to 2001 (50.2%). On the other hand, the percentage of patients receiving hormone therapy from 2003 to 2005 (81.1%) was almost the same as that from 1996 to 1998 (86.3%) and from 1999 to 2001 (89.7%). Compared with the PCS in the United States, patient characteristics and patterns of treatments from 2003 to 2005 have become more similar to those in the United States than those from 1996 to 1998 and those from 1999 to 2001.
Conclusions: This study indicates a trend toward increasing numbers of patients with early-stage disease and increasing proportions of patients treated with higher radiation doses with advanced equipment among Japanese prostate cancer patients treated with EBRT during 1996 to 2005 survey periods. Patterns of care for prostate cancer in Japan are becoming more similar to those in the United States. © **2010 Elsevier Inc.**

Patterns of care study, Prostate cancer, Radical external beam radiotherapy, Changing trend.

INTRODUCTION

The Patterns of Care Study (PCS) national survey is a retrospective study designed to establish the national practice process of therapies for selected malignancies over a specific time period (1–3). In addition to documenting the practice process, data from PCS surveys are important for developing and disseminating national guidelines for cancer treatment that help promote a more uniform care process in the country. The PCS is also designed to complement the role of clinical trials in enhancing the standard of care for cancer patients (1, 4).

To improve the quality of radiation oncology, PCS methodology has been imported to Japan from the United States. The Japanese PCS Working Group of Prostate Cancer started a nationwide process survey of patients treated with radiotherapy between 1996 and 1998 (5, 6). Subsequently, the Working Group conducted a second PCS of patients treated with radiotherapy between 1999 and 2001 and previously reported the results of this second PCS for prostate cancer patients in Japan treated with radiotherapy (7–18). At present, we have conducted a third PCS of patients treated with radiotherapy from 2003 to 2005 (19).

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Over the past 10 years, remarkable changes have occurred in prostate cancer treatment policy in Japan. The number of deaths due to prostate cancer has been on a steep increase, especially in elderly patients. The proportion of prostate cancer deaths to total cancer deaths also showed an increase from 0.9% in 1960 to 4.2% in 2000 (20). Since the introduction of prostate-specific antigen (PSA) screening, prostate cancer cases are being detected at earlier stages of disease, which allows early-stage patients a better chance of successful treatment and reduction of death from prostate cancer (21, 22). Moreover, recently, the use of radical external beam radiotherapy (EBRT) for prostate cancer has increased rapidly, as significant new radiation treatment planning technologies and methodologies have become available. Therefore, to optimally treat Japanese prostate cancer patients, it is important to accurately delineate the intrinsic changes taking place in the national practice process of radiotherapy for prostate cancer in Japan. In this report, we present the results of our analysis of the time-dependent transition of the process of care for prostate cancer patients treated with radical EBRT in the time periods from 1996 to 1998, 1999 to 2001, and 2003 to 2005.

METHODS AND MATERIALS

PCS surveys from 1996 to 1998, 1999 to 2001, and 2003 to 2005 in Japan contain detailed information about a total of 1,286 patients with prostate cancer treated with radiotherapy during the respective survey periods (307 patients were treated in 1996-1998; 387 patients in 1999-2001 PCS; and 592 patients in 2003-2005). PCS methodology has been described previously (1–4). Briefly, the PCS surveys were extramural audits that utilized a stratified two-stage cluster sampling design. The Japanese PCS used an original data format developed in collaboration with the American College of Radiology (Philadelphia, PA). The PCS surveyors consisted of 20 radiation oncologists from academic institutions. For each institution, one radiation oncologist collected data by reviewing patients' charts. To validate the quality of the collected data, the PCS used an Internet mailing list including all of the surveyors. On-site real-time checks and adjustments of the data input were available to each surveyor and to the PCS committee.

Of the 1,286 patients comprising the PCS 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys, patients with a diagnosis of adenocarcinoma of the prostate were eligible for inclusion in the present study unless they had one or more of the following conditions: (*1*) hormone-refractory cancer; (*2*) evidence of distant metastasis; (*3*) concurrent or prior diagnosis of any other malignancy; (*4*) prior radiotherapy; (*5*) or prior prostatectomy. In the current study, we considered the exclusion of patients with concurrent or prior diagnosis of nonmelanoma skin cancer would not affect the results of our PCS survey because the incidence of nonmelanoma skin cancers in Japan has been low compared to those in Western countries. A total of 841 patients with clinically localized prostate cancer treated with EBRT met these eligibility criteria and were selected for analysis (1996-1998 PCS included 161 patients from 51 institutions; 1999-2001 PCS included 283 patients from 66 institutions; and 2003-2005 PCS included 397 patients from 61 institutions). Criteria for institutional categories in the 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys have been detailed elsewhere (10, 11). Briefly, the PCS divided Japanese institutions into academic institutions (university hospital or cancer center) and nonacademic institutions (other hospitals).

In the current study, we used the risk groups utilized by D'Amico *et al.* (23), based on serum PSA level, biopsy, Gleason combined score, and 1992 American Joint Commission on Cancer (AJCC) clinical tumor category. Low-risk patients had a PSA of 10 μg/l or less, a Gleason score of 6 or less, and a 1992 tumor category of stage T1c or T2a. Intermediate-risk patients had PSA levels of 10.1 to 20 μg/l or a Gleason combined score of 7 or a 1992 AJCC tumor category of stage T2b. High-risk patients had a PSA level of more than 20 μg/l or a Gleason combined score of 8 or a 1992 AJCC tumor category of stage T2c.

Statistical analyses were performed using the Statistical Analysis System at the PCS data center at Osaka University (24). Statistical significance was tested using the chi-square test, Student's t test, and the Mann-Whitney U test. A probability level of 0.05 was chosen for statistical significance.

RESULTS

Patient characteristics

Patient characteristics for the PCS surveys from 1996 to 1998, 1999 to 2001, and 2003 to 2005 are shown in Table 1. There were significant increases over time in the proportion of patients with stage T1 to T2 disease (34.6% of patients in the 1996-1998 PCS; 48.2% of patients in the1999-2001 PCS; and 61.4% of patients in the 2003-2005 PCS) and decreases in median PSA values at diagnosis (: 22.0 ng/ml in the 1996-1998 PCS; 20.0 ng/ml in the 1999-2001 PCS; and 14.9 ng/ml in the 2003-2005 PCS). Data for the Gleason combined score were missing for 73.9% (119/161) of the patients in the 1996 to 1998 PCS and for 39.6% (112/283) of the patients in the 1999 to 2001 PCS, while only 5.5% (22/397) of patients were missing in the 2003 to 2005 PCS. The number of patients in the low-risk group increased gradually over time, while the number of patients in the high-risk group decreased gradually (Fig. 1). Table 1 and Fig. 2 indicate the reasons for selecting radiotherapy during these different time periods. There were significant increases over time in the number of patients treated with radiotherapy by their own choice (5.9% of patients in the 1996-1998 PCS; 26.5% of patients in the 1999-2001 PCS; and 41.4% of patients in the 2003-2005). This change in the rate of "patient choice" was significantly different ($p < 0.0001$).

Treatment characteristics

Treatment characteristics are shown in Table 2. The frequencies of radiation energies >10 MV, the use of portal or electronic portal images, and all field treatment each day increased gradually from 1996 to 1998 to 2003 to 2005. Also, the frequency of computed tomography (CT)-based treatment planning was 90.9% in 2003 to 2005, but 80.7% in 1996 to 1998, and 85.5% in 1999 to 2001. Moreover, the frequency of conformal therapy increased more rapidly from 2003 to 2005 (84.9%) than from 1996 to 1998 (49.1%) and 1999 to 2001 (50.2%).

Median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing up to 70 Gy from 2003 to 2005. Stratifying patients by

Table 1. Patient and disease characteristics

Patient characteristic	PCS survey 1996-1998 (n = 161 patients)	PCS survey 1999-2001 (n = 283 patients)	PCS survey 2003-2005 (n = 397 patients)	Significance (p value)
Institution	51	66	61	
Median age, years (range)	70.4 (46.5–89.8)	71.8 (49.7–92.2)	72.1 (50.7–87.7)	0.4556
Mean age ± SD	70.8 ± 8.1	71.8 ± 6.6	71.5 ± 6.1	0.3446
Median KPS % (range)	90 (40–100)	90 (50–100)	90 (60–100)	<0.0001
Mean ± SD	87.0 ± 8.9	89.1 ± 7.1	90.9 ± 8.5	<0.0001
Missing data	7	8	0	
Pretreatment PSA level (%)				
Median PSA level (range)	21.95 (0.3–900.0)	19.99 (0.6–856.9)	14.94 (0.7–3,058.0)	0.0176
Mean PSA level ± SD	51.5 ± 93.5	54.1 ± 99.5	48.2 ± 179.2	0.8719
<10	41/146 (28.1%)	77/268 (28.7%)	121/391 (30.9%)	0.0066
10-19.9	25/146 (17.1%)	57/268 (21.3%)	113/391 (28.9%)	
≥20	80/146 (54.8%)	134/268 (50.0%)	157/391 (40.2%)	
Missing data	15	15	6	
Lower pretreatment PSA level (%)				
<4	17/146 (11.6%)	8/268 (3.0%)	9/391 (2.3%)	<0.0001
≥4	129/146 (88.4%)	260/268 (97.0%)	382/391 (97.7%)	
Missing data	15	15	6	
Differentiation (no. patients/total) (%)				
Well	24/159 (15.1%)	62/264 (23.5%)	67/376 (17.8%)	0.0148
Moderate	79/159 (49.7%)	93/264 (35.2%)	152/376 (40.4%)	
Poor	46/159 (28.9%)	93/264 (35.2%)	99/376 (26.3%)	
Other	0/159 (0.0%)	2/264 (0.8%)	7/376 (1.9%)	
Unknown	10/159 (6.3%)	14/264 (5.3%)	51/376 (13.6%)	
Missing data	2	19	21	
Gleason combined score (%)				
2-6	11/42 (26.2%)	77/171 (45.0%)	118/375 (31.5%)	0.0014
7	18/42 (42.9%)	35/171 (20.5%)	134/375 (35.7%)	
8-10	13/42 (31.0%)	59/171 (34.5%)	123/375 (32.8%)	
Missing data	119	112	22	
T stage (no. patients/total) (%)				
TX-T0	1/159 (0.6%)	10/272 (3.7%)	1/394 (0.3%)	<0.0001
T1	8/159 (5.0%)	22/272 (8.1%)	88/394 (22.3%)	
T2	47/159 (29.6%)	109/272 (40.1%)	154/394 (39.1%)	
T3-T4	102/159 (64.2%)	124/272 (45.6%)	134/394 (34.0%)	
Unknown	1/159 (0.6%)	7/272 (2.6%)	17/394 (4.3%)	
Missing data	2	11	3	
N stage (no. patients/total) (%)				
NX-N0	136/157 (86.6%)	249/270 (92.2%)	372/394 (94.4%)	0.0038
N1	18/157 (11.5%)	15/270 (5.6%)	12/394 (3.0%)	
Unknown	3/157 (1.9%)	6/270 (2.2%)	10/394 (2.5%)	
Missing data	4	13	3	
Risk group (no. patients/total) (%)				
Low risk	1/127 (0.8%)	16/242 (6.6%)	40/381 (10.5%)	< 0.0001
Intermediate risk	7/127 (5.5%)	26/242 (10.7%)	107/381 (28.1%)	
High risk	119/127 (93.7%)	200/242 (82.6%)	234/381 (61.4%)	
Missing patient data	34	41	16	
Reason for selection of RT (no. patients/total) (%)				
Patient choice	8/136 (5.9%)	71/268 (26.5%)	159/384 (41.4%)	
Advanced or high-risk disease	43/136 (31.6%)	83/268 (31.0%)	121/384 (31.5%)	
Intercurrent disease	0/136 (0.0%)	0/268 (0.0%)	62/384 (16.1%)	
Medical contraindication	7/136 (5.1%)	36/268 (13.4%)	0/384 (0.0%)	
Old age	37/136 (27.2%)	44/268 (16.4%)	94/384 (24.5%)	
Other	9/136 (6.6%)	8/268 (3.0%)	6/384 (1.6%)	
NA or unknown	32/136 (23.5%)	26/268 (9.7%)	27/384 (7.0%)	
Missing data	25	15	13	

Abbreviations: KPS = karnofsky performance status; PSA = prostate-specific antigen; RT = radiotherapy; NA = data not available; SD = standard deviation.

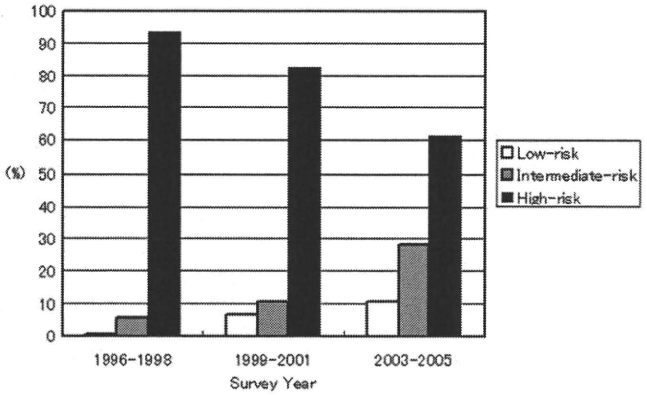

Fig. 1. Distribution of patients with prostate cancer according to risk group among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

total dosage revealed that 24.8% of patients received total radiation doses below 60 Gy in the 1996 to 1998 PCS, decreasing to only 2.0% from 2003 to 2005. Also, only 17.4% of patients received total doses of >70 Gy from 1996 to 1998, which increased dramatically to 52.0% from 2003 to 2005 (Fig. 3). Increased radiation doses were administered predominantly in academic institutions (Table 2).

The percentage of patients receiving hormone therapy from 2003 to 2005 (81.1%) was almost the same as that from 1996 to 1998 (86.3%) and that from 1999 to 2001 (89.7%). Hormonal therapy was used before, during, and after radiotherapy for a mean duration of 30.1 ± 29.8 months, 43.9 ± 36.7 months, and 40.6 ± 34.3 months, respectively (86.3% of patients in 1996-1998; 89.7% of patients in 1999-2001; and 81.1% in 2003-2005). The proportion of patients receiving hormone therapy was analyzed according to risk group. Most patients in the intermediate- and high-risk groups were treated with hormone therapy during 1996 to 1998, 1999 to 2001, and 2003 to 2005 survey periods (Fig. 4). In the low risk-group, approximately 50% to 70% of patients were treated with hormone therapy in the periods 1999 to 2001 and 2003 to 2005. We could not precisely analyze the incidence of low-risk patients treated with hormone therapy during the 1996 to 1998 period because only 1 patient, who was not treated with hormone therapy, was available for this analysis.

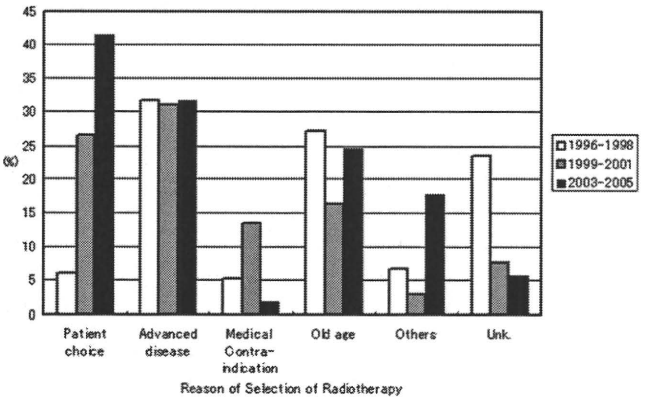

Fig. 2. Reasons of selection of EBRT for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

FTE radiation oncologists

For academic institutions, the mean numbers of full-time equivalent (FTE) radiation oncologists increased gradually over time (results of the surveys for 1996-1998, 1999-2001, and 2003-2005 were 2.13, 2.36, and 2.86, respectively). For nonacademic institutions, the mean numbers of FTE radiation oncologists also increased gradually over time (results for 1996-1998, 1999-2001, and 2003-2005 were 0.57, 0.62, and 0.75, respectively), but the numbers were extremely low compared with those in academic institutions.

Comparisons of changing trends in patient and treatment characteristics between Japan and the United States

Changing trends between Japan and the United States were analyzed with regard to patient and treatment characteristics by using the US PCS data reported by Zelefsky *et al.* (25). In Japan, the proportions of patients with stage T3 to T4 disease and PSA levels >20 ng/ml decreased gradually from 1996 to 1998 to 2003 to 2005, but the proportions of patients with T3 to T4 disease, a Gleason score of 8 to 10, and a PSA level of >20 ng/ml were over 30% among the three surveys (Fig. 5a). On the other hand, in the United States, the proportions of patients with T3 to T4 disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were almost the same, and the proportions of patients with T3 to T4 disease, a PSA of >20 ng/ml, and a Gleason score of 8 to 10 were approximately 20% or less during the survey period (Fig.5b).

Regarding treatment characteristics, in Japan, the proportions of patients receiving conformal radiotherapy and higher radiation doses (72 Gy or more) increased, as 84.9% of patients were treated with conformal therapy, and 16.9% of patients were treated with higher radiation doses in 2003 to 2005. On the other hand, use of hormone therapy was over 80% during the survey periods (Fig.6a). In the United States, the proportions of patients receiving hormone therapy and higher radiation doses (72 Gy or more) increased continuously over the survey periods, and the proportions of patients receiving hormone therapy and higher radiation doses were approximately 45% to 50% (Fig. 6b). Concerning conformal therapy in the United States, 80% of patients were treated with conformal radiotherapy in 1999, which was almost the same frequency as patients treated from 2003 to 2005 in Japan.

DISCUSSION

Results of the current study indicate that there were significant increases in the proportions of prostate cancer patients with stage T1 to T2 disease and lower initial PSA values in the 1996 to 2005 survey periods in Japan. Numbers of patients in the low-risk group increased gradually, while

Table 2. Treatment characteristics

Treatment	PCS survey 1996-1998 (n = 161)	1999-2001 (n = 283)	2003-2005 (n = 397)	Significance (p value)
Received radiotherapy				
Energy (≥10 MV) (%)				
Yes (no. patients/total) (%)	98/161 (60.9%)	208/279 (74.6%)	312/386 (80.8%)	<0.0001
Missing data	0	4	11	
Portal films or electric portal images used (%)				
Yes (no. patients/total) (%)		210/280 (75.4%)	388/397 (97.7%)	<0.0001
Missing data		3	0	
All fields treated each day (%)				
Yes (no. patients/total) (%)	44/65 (67.7%)	215/283 (76.0%)	363/397 (91.4%)	<0.0001
Missing data	96	0	0	
CT-based treatment planning (%)				
Yes (no. patients/total) (%)	130/161 (80.7%)	241/282 (85.5%)	361/397 (90.9%)	0.0006
Missing	0	1	0	
Received conformal radiotherapy (%)				
Yes (no. patients/total) (%)	79/161 (49.1%)	142/283 (50.2%)	337/397 (84.9%)	<0.0001
Received pelvic irradiation (%)				
Yes (no. patients/total) (%)	69/161 (42.9%)	102/283 (36.0%)	95/397 (23.9%)	<0.0001
Radiation dose (cGy)				
A+B (total)				
Median (range)	6,500 (2,200–7,400)	6,840 (1,400–8,200)	7,000 (800–8,410)	<0.0001
Mean ± SD	6,090.9 ± 990.5	6,602.9 ± 731.1	6,764.0 ± 621.9	<0.0001
A median (min-max)	6,500 (2,200–7,400)	6,600 (1,400–8,200)	7,000 (800–8,410)	<0.0001
Mean ± SD	6,250.9 ± 976.8	6,610.3 ± 766.5	6,855.8 ± 708.0	<0.0001
B median (min-max)	5,940 (3,400–7,000)	6,900 (3,000–8,000)	6,600 (3,000–7,640)	<0.0001
Mean ± SD	5,622.4 ± 885.6	6,592.6 ± 681.9	6,654.9 ± 480.5	<0.0001
Prescription dose levels (Gy) (no. patients/total) (%)				
<60	40/161 (24.8%)	17/282 (6.0%)	8/396 (2.0%)	<0.0001
60-65	36/161 (22.4%)	56/282 (19.9%)	57/396 (14.4%)	
65-70	57/161 (35.4%)	102/282 (36.2%)	125/396 (31.6%)	
≥70	28/161 (17.4%)	107/282 (37.9%)	206/396 (52.0%)	
Missing data	0	1	1	
Higher prescription dose levels (no. patients/total) (%)				
<72	159/161 (98.8%)	261/282 (92.6%)	329/396 (83.1%)	<0.0001
≥72	2/161 (1.2%)	21/282 (7.4%)	67/396 (16.9%)	
Missing data	0	1	1	
Received hormone therapy (%)				
Yes (no. patients/total) (%)	138/160 (86.3%)	253/282 (89.7%)	321/396 (81.1%)	0.0284
No (no. patients/total) (%)	21/160 (13.1%)	29/282 (10.3%)	73/396 (18.4%)	
Unknown	1/160 (0.6%)	0/282 (0.0%)	2/396 (0.5%)	
Missing data	1	1	1	
Received chemotherapy				
Yes (no. patients/total) (%)	20/159 (12.6%)	17/274 (6.2%)	5/394 (1.3%)	<0.0001
No (no. patients/total) (%)	137/159 (86.2%)	255/274 (93.1%)	387/394 (98.2%)	
Unknown	2/159 (1.3%)	2/274 (0.7%)	2/394 (0.5%)	
Missing data	2	9	3	

Abbreviation: SD = standard deviation.

numbers of patients in the high-risk group decreased gradually. These results suggest that the likelihood of early-stage prostate cancer patients being treated with radiotherapy is greater than ever before in Japan. In the United States, most of the prostate cancer patients have early-stage tumors, and radiotherapy has been recognized as the first-line therapy for prostate cancer (25–28). Because of the prevailing use of PSA screening and the increasing number of patients treated with radiotherapy in Japanese institutions (29), the opportunities for treating early-stage prostate cancer patients with radical EBRT should increase even more in the future.

In the current study, the data for a Gleason combined score were missing for 73.9% of the patients in the 1996 to 1998 PCS and 39.6% of the patients in the 1999 to 2001 PCS, while data for only 5.5% of the patients in 2003 to 2005 PCS were missing. These results suggest that previously in Japan, physicians did not realize the importance of the

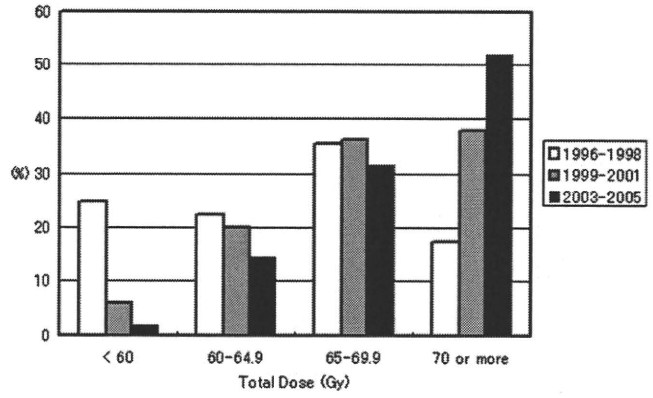

Fig. 3. Distributions of total radiation doses of external beam radiotherapy for patients with prostate cancer among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

Gleason combined score, but recently, they are becoming aware that the Gleason combined score is of critical importance in the evaluation and management of prostate cancer patients. Further studies are required to confirm whether physicians in Japan will routinely use the Gleason combined score in the management of prostate cancer patients in future.

The current study also revealed a remarkable change in the reason for choosing radiotherapy in Japan among the 1996 to 2005 survey periods. Only 5.9% of the patients were treated with radiotherapy by their own choice from 1996 to 1998, but 41.4% of patients chose radiotherapy from 2003 to 2005. EBRT did not become a popular treatment modality for prostate cancer in Japan until the end of the 1990s. A strong surgical tradition and an insufficient number of radiation oncology centers capable of delivering appropriate treatment prevented earlier dissemination of this type of therapy. However, in conjunction with significant improvements in the availability of new radiation treatment planning technologies and methodologies for treatment planning and delivery, Japanese patients are becoming increasingly aware of the effectiveness of radiotherapy for prostate cancer (30, 31). Therefore, the increasing percentage of patients choosing radiotherapy might reflect a growing acceptance of radical external EBRT as one of the main treatments for prostate cancer patients in Japan.

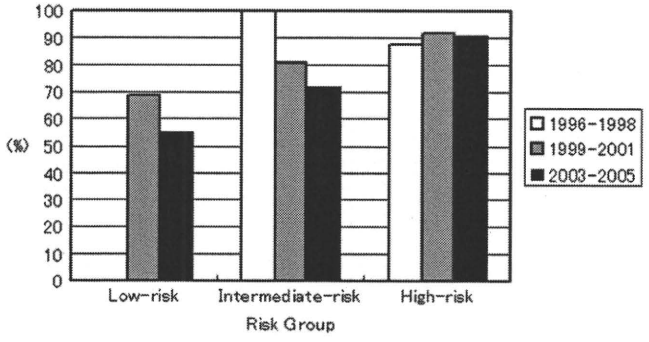

Fig. 4. Hormonal therapy distribution according to risk group for prostate cancer in Japan among 1996-1998, 1999-2001, and 2003-2005 Japanese PCS surveys.

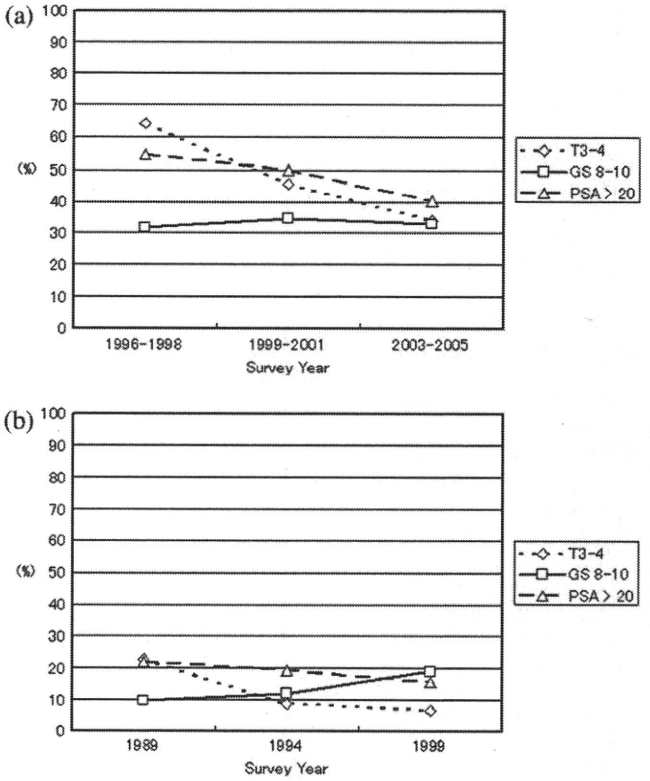

Fig. 5. (a) Changing trend in patient characteristics in Japan. (b) Changing trend in patient characteristic in the United States. (Data from ZelefskyMJ, Moughan J, Owen J, et al. Changing trends in national practice for external beam radiotherapy for clinically localized prostate cancer: 1999 patterns of care survey for prostate cancer. Int J Radiat Oncol Biol Phys 2004;59:1053-1061)

Moreover, the radiotherapy strategy appears to have changed among the 1996 to 1998, 1999 to 2001, and 2003 to 2005 survey periods. The frequency of CT-based treatment planning increased up to 90.9% in 2003 to 2005, and the usage of conformal therapy increased rapidly from 2003 to 2005 (84.9%). The median radiation doses were 65.0 Gy and 68.4 Gy from 1996 to 1998 and from 1999 to 2001, respectively, increasing up to 70 Gy from 2003 to 2005. Also, the proportions of patients receiving total radiation doses below 60 Gy decreased, while the proportions of patients receiving total doses of >70 Gy increased rapidly during the survey period (Fig. 3). These results indicate that patients receiving lower radiation doses with obsolete treatment equipment was more common between 1996 and 1998, while higher doses with high-technology radiation equipment prevailed between 2003 and 2005. US PCS results indicate that many prostate cancer patients have been routinely treated with total doses of >70 Gy in the United States (25, 28). The use of increasing radiation doses in Japan might reflect the widespread dissemination of clinical trial results (32–35) and also a growing acceptance by radiation oncologists and urologists that radical EBRT is effective for treating prostate cancer (30, 31).

Results of the current study indicate that hormone therapy was commonly used in conjunction with radiotherapy during the survey period in Japan. Moreover, it was not only

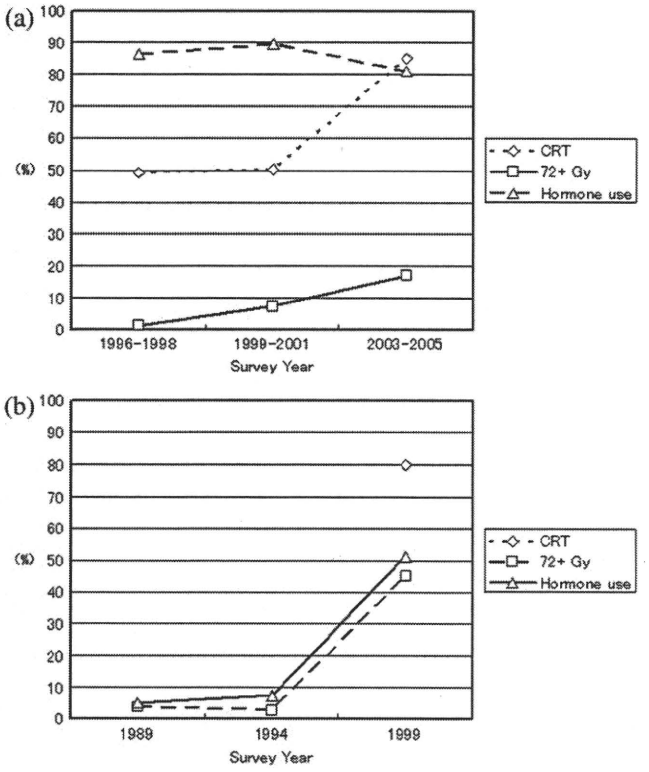

Fig. 6. (a) Changing trend in treatment characteristics in Japan. (b) Changing trend in patient characteristics in the United States. (*Data from* Schröder FH, Hugosson J, Roobol MJ, *et al.* Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320-1328.)

patients in the intermediate- and high-risk groups but also patients in the low-risk group who were frequently treated with hormone therapy during 1999 to 2001 and 2003 to 2005 (Fig. 4). However, several studies from the United States have indicated that radical radiotherapy alone could control the disease in low-risk patients. Zietman *et al.* (34) indicated that a total dose of 70 Gy was sufficient to control the disease when the pretreatment PSA level was less than 10 ng/ml. Hanks *et al.* (35) found that prostate cancer patients with a pretreatment PSA level of <10 ng/ml did not benefit from a dose escalation above 70 Gy (35). Therefore, radical EBRT without hormone therapy has been the primary treatment for patients in the United States with low-risk diseases. The high rate of health insurance coverage for Japanese people may explain the frequent administration of hormone therapy in Japan (36). Another reason may be that at present, many Japanese radiation oncologists may consider the higher dose levels (>72 Gy) unnecessary for prostate cancer patients when combined with long-term hormone therapy. Therefore, radical EBRT without hormone therapy should also be the treatment of choice for low-risk patients in Japan.

In the current study, the mean numbers of FTE radiation oncologists increased gradually over time in both academic and nonacademic institutions. However, the median number of FTE radiation oncologists remained low, especially in nonacademic institutions. Publication data documenting a progressive increase in the number of prostate cancer patients treated with radiotherapy in every institution, demonstrating a need for both academic and nonacademic Japanese institutions to upgrade their radiation equipment and to recruit more radiation oncologists (29).

Changing trends between Japan and the United States were analyzed with regard to patient and treatment characteristics. In Japan, proportions of patients with T3 to T4 disease, a Gleason score of 8 to 10, and a PSA level of >20 ng/ml were all over 30%, but proportions of patients with T3 to T4 disease and a PSA level of >20 ng/ml decreased gradually during the survey period (Fig. 5a). In the United States, the proportions of patients with T3 to T4 stage disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were almost the same, and the proportions of patients with T3 to T4 stage disease, a PSA level of >20 ng/ml, and a Gleason score of 8 to 10 were approximately 20% or less during the survey period (Fig.5b). These results indicate that although patients in Japan had more advanced disease than those in the United States, patient characteristics in Japan have been changing, becoming more similar to patients in the United States. Further studies are required to confirm this finding.

Concerning treatment characteristics: in Japan, proportions of patients receiving conformal radiotherapy and higher radiation doses have been increasing, and 84.9% of patients were treated with conformal therapy, and 16.9% of patients were treated with higher radiation doses in 2003 to 2005 (Fig. 6a). In the United States, conformal therapy was administered to 85% of patients in 1999, and higher radiation doses (72 Gy or more) have increased continuously from 1989 to 1999 (Fig. 6b). These results indicate that although radiotherapy characteristics were still developing in Japan compared to the United States, the proportions of modern radiotherapy have been increasing both in Japan and the United States during the survey period.

The percentage of patients receiving hormone therapy remained high during the periods from 1996 to 1998 to 2003 to 2005 in Japan. On the other hand, there was a rapid increase in the use of hormone therapy in the United States from 1994 to 1999. The significantly increased use of hormone therapy for high-risk patients in the United States reflects the penetration and growing acceptance of clinical trial results that have demonstrated the efficacy of these treatment approaches (32, 33). The randomized Radiation Therapy Oncology Group 8610 trial demonstrated an increase in disease-free survival at 2 years (76% vs. 62% survival) for locally advanced prostate cancer patients treated with neoadjuvant total androgen blockade plus radiation compared to those treated with radiation therapy alone (33). In Japan, hormone therapy was administered to approximately 90% of patients with high-risk disease, and these high rates of hormone therapy have continued for several years. Therefore, radiotherapy in conjunction with hormone therapy appears to be an accepted approach for the unfavorable risk group in Japan and in the United States.

CONCLUSIONS

By comparing the PCS results of 1996 to 1998, 1999 to 2001, and 2003 to 2005 surveys, we can delineate changes in the process of care for prostate cancer patients treated with radiotherapy in Japan. Study data indicate a trend toward increasing early-stage disease and increasing proportions of patients treated with higher radiation doses with advanced equipments, suggesting that radical EBRT is gaining acceptance as a first-line treatment for prostate cancer in Japan. Also, our results indicate that patterns of care for prostate cancer in Japan are becoming more similar to those in the United States. In the future, to optimize the delivery of radiotherapy, more advanced equipment and more FTE radiation oncologists are warranted. Also, repeat surveys and point-by-point comparisons of results from other countries, such as the United States, will demonstrate how EBRT for prostate cancer has been developed and optimized for patients in Japan.

REFERENCES

1. Hanks GE, Coia LR, Curry J. Patterns of care studies: past, present and future. *Semin Radiat Oncol* 1997;7:97–100.
2. Owen JB, Sedransk J, Pajak TF. National averages for process and outcome in radiation oncology: Methodology of the patterns of care study. *Semin Radiat Oncol* 1997;7:101–107.
3. Tanisada K, Teshima T, Ohno Y, *et al.* Patterns of care study quantitative evaluation of the quality of radiotherapy in Japan. *Cancer* 2002;95:164–171.
4. Teshima T. Patterns of care study in Japan. *Jpn J Clin Oncol* 2005;35:497–506.
5. Nakamura K, Teshima T, Takahashi Y, *et al.* Radical radiotherapy for prostate cancer in Japan: A pattern of care study report. *Jpn J Clin Oncol* 2003;33:122–126.
6. Nakamura K, Teshima T, Takahashi Y, *et al.* Radiotherapy for localized hormone-refractory prostate cancer in Japan. *Anticancer Res* 2004;24:3141–3145.
7. Nakamura K, Ogawa K, Yamamoto T, *et al.* Trends in the practice of radiotherapy for localized prostate cancer in Japan: a preliminary patterns of care study report. *Jpn J Clin Oncol* 2003; 33:527–532.
8. Ogawa K, Nakamura K, Sasaki T, *et al.* Radical external beam radiotherapy for prostate cancer in Japan: Preliminary results of the 1999-2001 patterns of care process survey. *Jpn J Clin Oncol* 2004;34:29–36.
9. Ogawa K, Nakamura K, Sasaki T, *et al.* Radical external beam radiotherapy for prostate cancer in Japan: preliminary results of the changing trends in the patterns of care process survey between 1996-1998 and 1999-2001. *Jpn J Clin Oncol* 2004;34: 131–136.
10. Ogawa K, Nakamura K, Onishi H, *et al.* Radical external beam radiotherapy for clinically localized prostate cancer in Japan: Changing trends in the patterns of care process survey between 1996-1998 and 1999-2001. *Anticancer Res* 2005;25:3507–3511.
11. Ogawa K, Nakamura K, Onishi H, *et al.* Radical external beam radiotherapy for prostate cancer in Japan: Results of the 1999-2001 patterns of care process survey. *Jpn J Clin Oncol* 2006;36: 40–45.
12. Ogawa K, Nakamura K, Onishi H, *et al.* Influence of age on the pattern and outcome of external beam radiotherapy for clinically localized prostate cancer. *Anticancer Res* 2006;26: 1319–1325.
13. Ogawa K, Nakamura K, Onishi H, *et al.* Radical external beam radiotherapy for clinically localized prostate cancer in Japan: Differences in the patterns of care between Japan and the United States. *Anticancer Res* 2006;26:575–580.
14. Sasaki T, Nakamura K, Ogawa K, *et al.* Postoperative radiotherapy for patients with prostate cancer in Japan: Changing trends in national practice between 1996-98 and 1999-2001: Patterns of care study for prostate cancer. *Jpn J Clin Oncol* 2006;36:649–654.
15. Ogawa K, Nakamura K, Sasaki T, *et al.* Radical external beam radiotherapy for prostate cancer in Japan: Differences in the patterns of care among Japan, Germany, and the United States. *Radiat Med* 2008;26:57–62.
16. Ogawa K, Nakamura K, Sasaki T, *et al.* External beam radiotherapy for clinically localized hormone-refractory prostate cancer: clinical significance of nadir prostate-specific antigen value within 12 months. *Int J Radiat Oncol Biol Phys* 2009; 74:759–765.
17. Sasaki T, Nakamura K, Ogawa K, *et al.* Radiotherapy for patients with localized hormone-refractory prostate cancer: results of the Patterns of Care Study in Japan. *BJU Int* 2009; 104:1462–1466.
18. Ogawa K, Nakamura K, Sasaki T, *et al.* Postoperative radiotherapy for localized prostate cancer: Clinical significance of nadir prostate-specific antigen value within 12 months. *Anticancer Res* 2009;29:4605–4613.
19. Nakamura K, Ogawa K, Sasaki T, *et al.* Patterns of radiation treatment planning for localized prostate cancer in Japan: 2003-05 patterns of care study report. *Jpn J Clin Oncol* 2009; 39:820–824.
20. Yoshimi I, Mizuno S. Cancer Statistics Mortality trends of prostate cancer in Japan: 1960-2000. *Jpn J Clin Oncol* 2003; 33:367.
21. Schröder FH, Hugosson J, Roobol MJ, *et al.* Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320–1328.
22. Andriole GL, Crawford ED, Grubb RL III, *et al.* Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310–1319.
23. D'Amico AV, Schultz D, Loffredo M, *et al.* Biochemical outcome following external beam radiation therapy with or without androgen suppression therapy for clinically localized prostate cancer. *JAMA* 2000;284:1280–1283.
24. SAS procedure reference, version 6. 1st ed. Tokyo: SAS Institute Iin Japan; 1995.
25. Zelefsky MJ, Moughan J, Owen J, *et al.* Changing trends in national practice for external beam radiotherapy for clinically localized prostate cancer: 1999 patterns of care survey for prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;59:1053–1061.
26. Chuba PJ, Moughan J, Forman JD, *et al.* The 1989 patterns of care study for prostate cancer: Five-year outcomes. *Int J Radiat Oncol Biol Phys* 2001;50:325–334.
27. Zietman A, Moughan J, Owen J, *et al.* The patterns of care survey of radiation therapy in localized prostate cancer: similarities between the practice nationally and in minority-rich areas. *Int J Radiat Oncol Biol Phys* 2001;50:75–80.
28. Hanks GE, Teshima T, Pajak TF. 20 years of progress in radiation oncology: Prostate cancer. *Semin Radiat Oncol* 1997;7: 114–120.
29. Imai A, Teshima T, Ohno Y, *et al.* The future demand for and structural problems of Japanese radiotherapy. *Jpn J Clin Oncol* 2001;31:135–141.

30. Takahashi A, Yanase M, Masumori N, *et al.* External beam radiation monotherapy for localized or locally advanced prostate cancer. *Jpn J Clin Oncol* 2003;33:73–77.
31. Sasaki T, Nakamura K, Shioyama Y, *et al.* Efficacy of modest dose irradiation in combination with long-term endocrinal treatment for high-risk prostate cancer: A preliminary report. *Jpn J Clin Oncol* 2004;34:420–424.
32. Bolla M, Gonzalez D, Warde P, *et al.* Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295–300.
33. Pilepich MV, Caplan R, Byhardt RW, *et al.* Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of Radiation Therapy Oncology Group protocol 85-31. *J Clin Oncol* 1997;15:1013–1021.
34. Zietman AL. Radiation therapy or prostatectomy: an old conflict revisited in the PSA era; A radiation oncologist's viewpoint. *Semin Radiat Oncol* 1998;8:81–86.
35. Hanks GE, Schultheiss TE, Hanlon AL, *et al.* Optimization of conformal radiation treatment of prostate cancer: Report of a dose escalation study. *Int J Radiat Oncol Biol Phys* 1997; 37:543–550.
36. Takara K. The origins and development of public health in Japan. In: Detels R, McEwen J, Omenn GS, editors. The scope of public health. *Oxford textbook of public health.* 3rd edition, vol. 1. New York: Oxford University Press; 1997. p. 55–72.

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CLINICAL INVESTIGATION **Pancreas**

INTRAOPERATIVE RADIOTHERAPY FOR RESECTED PANCREATIC CANCER: A MULTI-INSTITUTIONAL RETROSPECTIVE ANALYSIS OF 210 PATIENTS

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Purpose: To retrospectively analyze the results of intraoperative radiotherapy (IORT) with or without external beam radiotherapy (EBRT) for resected pancreatic cancer.
Methods and Materials: The records of 210 patients treated with gross complete resection (R0: 147 patients; R1: 63 patients) and IORT with or without EBRT were reviewed. One hundred forty-seven patients (70.0%) were treated without EBRT and 114 patients (54.3%) were treated in conjunction with chemotherapy. The median doses of IORT and EBRT were 25 Gy (range, 20–30 Gy) and 45 Gy (range, 20–60Gy), respectively. The median follow-up of the surviving 62 patients was 26.3 months (range, 2.7–90.5 months).
Results: At the time of this analysis, 150 of 210 patients (71.4%) had disease recurrences. Local failure was observed in 31 patients (14.8%), and the 2-year local control rate in all patients was 83.7%. The median survival time and the 2-year actuarial overall survival (OS) in all 210 patients were 19.1 months and 42.1%, respectively. Patients treated with IORT and chemotherapy had a significantly more favorable OS than those treated with IORT alone ($p = 0.0011$). On univariate analysis, chemotherapy use, degree of resection, carbohydrate antigen 19-9, and pathological N stage had a significant impact on OS and on multivariate analysis; these four factors were significant prognostic factors. Late gastrointestinal morbidity of NCI-CTC Grade 4 was observed in 7 patients (3.3%).
Conclusion: IORT yields an excellent local control rate for resected pancreatic cancer with few frequencies of severe late toxicity, and IORT combined with chemotherapy confers a survival benefit compared with that of IORT alone.

Radiotherapy, Intraoperative radiotherapy, Pancreatic neoplasms, Complete resection.

INTRODUCTION

Pancreatic cancer is one of the leading causes of cancer death worldwide. The prognosis of patients with this disease remains extremely poor, with a 5-year survival rate after diagnosis of less than 5%. Only a small percentage of patients (10–20%) are candidates for surgical resection (1–3). However, even if curative resection is performed, 5-year survival rates are approximately 10–20%, and approximately 50% of patients experience local recurrence after gross complete resection (4–6). The high rate of local recurrence after surgery is most likely due to the frequent presence of residual microscopic disease, which generally requires higher doses of external beam radiotherapy (EBRT) with standard fractionation (7). Therefore, integrated therapy represents an important strategy for improving the prognosis of this disease.

Intraoperative radiotherapy (IORT) is an attractive strategy to reduce the risk of local recurrence after surgical resection in cases where tumors are operable. This technique allows for administration of a single high dose of ionizing radiation during the surgical intervention targeted at the surgical bed to eliminate any microscopic remains of tumor, and it has the advantage of enabling healthy tissues to be displaced and

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