Table 5. Nuclear Size of Histologic Typing in Patients With Small Adenocarcinoma of the Lung With 5-Year Survival Rate

Type	No. of Patients	NA, Mean±SD, μm^2	*P*	ND, Mean±SD, μm	*P*	5-Year Survival, %	Log-Rank *P*
Lepidic type							
A	12	47±7	.008 (A-C)	8.9±0.6	.001 (A-C)	100	
B	14	51±15		9.4±1.4		100	
C	66	63±15		10.4±1.2		73	
Nonlepidic type							
D	27	77±18	.002 (vs C)	11.2±1.2	.034 (vs C)	70	
E	8	67±10		10.7±0.9		75	
F	6	64±15		10.3±1.3		83	
Types A and B	26	49±12	<.0001	9.2±1.1	<.0001	100	.018
Type C	66	63±15	.005	10.4±1.2	.035	73	
Types D, E, and F	41	73±17		11.0±1.2		73	
Lepidic type	92	59±16	<.0001	10.0±1.2	<.0001	80	.288
Nonlepidic type	41	73±17		11.0±1.2		73	

NA indicate nuclear area; SD, standard deviation; ND, nuclear major axis dimension.
Adapted from Noguchi et al.[5]

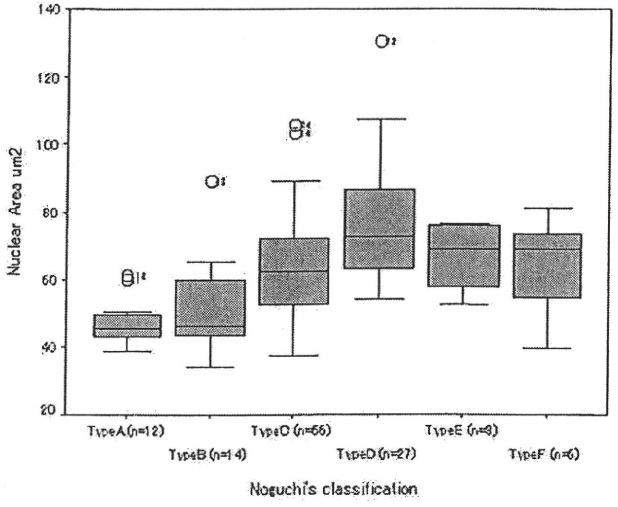

Figure 5. A box plot of the nuclear area in all patients is shown, classified according to the Noguchi classification.

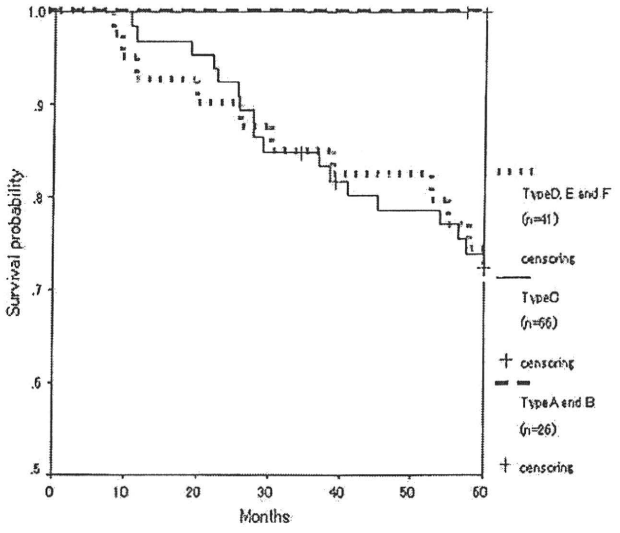

Figure 6. The 5-year recurrence-free survival rates of all patients is shown, classified according to the modified Noguchi classification with 3 subtypes: types A and B (n = 26), type C only (n = 66), and nonlepidic type (types D, E, and F; n = 41).

size parameters of small lymphocytes were nuclear area 14 ± 4 μm^2 and nuclear diameter 3.9 ± 0.03 μm, the critical nuclear area level of 67 μm^2 was approximately 5× larger than that of lymphocytes,[6] and the critical nuclear diameter level of 10.7 μm was approximately 3× larger. The mean (±SD) value of the kappa statistic for the 4 pathologists was 0.58 ± 0.10 (range, 0.47-0.76), and the mean (±SD) value of the accuracy metric was 0.66 ± 0.10 (range, 0.56-0.80).

DISCUSSION

In 1987, the potential role of morphometry in surgical pathology was reported by Paplanus et al,[7] who indicated that morphometry could be specifically helpful for 1) identifying malignant cells in lesions that are largely composed of apparently benign cells (eg, follicular thyroid neoplasms), 2) defining reference points in apparent continua (eg, in the progression from normal colon tissue to adenoma to adenocarcinoma), 3) distinguishing between benign and malignant lesions with similar appearances (eg, fibromatosis and soft tissue fibrosarcoma), and 4) distinguishing between malignant neoplasms of a similar appearance (eg, small-cell carcinoma of the lung and

small-cell lymphoma). Many studies have performed quantitative assessment of nuclear morphometry in pulmonary malignant tumors as an adjunct to the diagnostic and prognostic work of pathologists.[6,10-13] However, no study has established prognostic cutoff points based on nuclear morphology. Of course, a small fraction of tumor cells in S-G2 phase may show a larger nuclear size, and some nuclei may not be sectioned through the largest dimension. Therefore, the data obtained in these experiments did not necessarily reflect the accurate size of the nuclei. However, we focused on estimating the malignancy of the tumors based on nuclear morphometry, and not on the accurate nuclear size.

In the present study, ROC curve analysis showed that a cutoff nuclear area of 67 μm^2 had 75% sensitivity and 70% specificity, and that a nuclear diameter of 10.7 μm had 75% sensitivity and 65% specificity for detecting malignant strictures, respectively. Furthermore, it was proved that the 5-year survival rate of both groups was significantly different by log-rank test ($P < .001$) (Fig. 3). Table 2 shows that the most significant prognostic and staging factors for all the subtypes of small-sized pulmonary adenocarcinoma were significantly associated with nuclear area and nuclear diameter. Furthermore, multivariate analysis demonstrated that nuclear area was a significant prognostic determinant ($P = .037$). These results indicated that small-sized adenocarcinomas can be divided into 2 groups: those showing an extremely favorable prognosis (5-year survival rate around 90%) and those showing a fairly favorable prognosis (5-year survival rate around 60%-70%). The former group showing a 90% 5-year survival rate may be regarded as having minimally invasive carcinoma; members are candidates for reduction or limited surgery, similarly to early stage gastric carcinoma, which is treatable by endoscopic surgery.

It is of considerable practical interest that pathologists can extract cases showing an extremely favorable prognosis using only morphometric calculation of nuclear area or nuclear diameter for each tumor. To select patients eligible for limited surgery, it is not necessary to examine histological structures such as those of the papillary, acinar, and solid subtypes. Of course, nuclear area and nuclear diameter status are associated with the ratio of the lepidic growth area and Noguchi's classification, which are purely structural classifications. For example, Noguchi's classification reflects the prognosis of small-sized adenocarcinomas of the lung. Figure 5 indicates that the nuclear area of type C tumors was significantly larger than that of type A tumors ($P < .0001$). Conversely, the nuclear area of type D tumors was significantly larger than that of type C tumors ($P < .002$). As the 5-year survival rate of patients with type A tumors was better than that of patients with type C tumors, and that of patients with type C tumors was better than that of patients with type D tumors, the prognostic significance of the mean nuclear areas of these tumors coincides with Noguchi's classification. By using small biopsy specimens, it is sometimes very difficult to make an accurate histological diagnosis. However, if oncologists can obtain information from thin-slice computed tomography examinations that allow calculation of the lepidic growth component ratio of the tumor, together with nuclear morphometry data from biopsy specimens, it would be very practical to extract candidate patients who would benefit from limited treatment before carrying out surgery. In practical terms, we cannot use the Image Processor for Analytical Pathology in routine pathology examinations. We recommend that the size of intermingled small lymphocytes be used as an internal control. Tumor cells with a nuclear area of ≥ 67 μm^2 and a nuclear diameter of 10.7 μm are 5× and 3× larger than small lymphocytes, respectively.

Grading of nuclear structure has already been used to assess the malignancy of various carcinomas, such as breast carcinoma, urinary bladder carcinoma, and renal cell carcinoma. For example, after Zajdela et al[8] reported the relationship between the outcome of mammary cancer and morphological characteristics using cytological materials, several studies demonstrated the prognostic value of nuclear morphometry in invasive ductal carcinoma of the breast. Nuclear morphology is now applied for histological grading of invasive breast carcinomas in the WHO Classification of Tumors of the Breast.[14] The WHO recommends that nuclear grade be included in the surgical reports of cases of invasive ducal carcinoma of the breast. In the present study, we demonstrated that nuclear area and nuclear diameter can also be used to estimate the malignant potential of small-sized adenocarcinomas of the lung.

We stress the importance of nuclear area and nuclear diameter for estimating the malignancy of small-sized adenocarcinomas of the lung. If nuclear grading can be applied along with a pure histological classification such as the WHO or Noguchi classifications, then it may be possible to predict the biological behavior of small-sized adenocarcinomas more precisely than on the basis of histological classification.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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Survival Differences by Gender for Resected Non-small Cell Lung Cancer

A Retrospective Analysis of 12,509 Cases in a Japanese Lung Cancer Registry Study

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Introduction: Women with non-small cell lung cancer (NSCLC) are more likely to have better survival than men. This study intended to assess gender differences in the survival of these patients in a large registry population.

Methods: In 2005, the Japanese Joint Committee for Lung Cancer Registration performed a nationwide retrospective registry study regarding the prognosis and clinicopathologic profiles of patients who underwent resection for primary lung neoplasms in 1999. The registry data of 12,509 patients with NSCLC were analyzed in terms of gender differences in prognosis and clinicopathologic features.

Results: There were 8353 (66.8%) men and 4156 (33.2%) women with a mean age at operation of 66.4 and 65.0 years, respectively ($p < 0.001$). Women had a higher incidence of adenocarcinoma ($p < 0.001$) and stage IA disease ($p < 0.001$) than men. The overall survival was significantly better in women than men. The 5-year survival rates (5-YSRs) for women and men were 75.6 and 57.9%, respectively ($p = 0.0000$). According to histology, the overall survival of women was significantly better than that of men for both adenocarcinoma (5-YSR, 77.7 versus 61.9%, $p = 0.0000$) and nonadenocarcinoma (5-YSR, 59.3 versus 53.1%, $p = 0.035$). In adenocarcinoma, women had a significantly better prognosis than men for pathologic stage I/II disease. However, in nonadenocarcinoma, there was no significant prognostic difference between the two genders in pathologic stage I/II disease.

Conclusions: Women with NSCLC, especially with an adenocarcinoma histology, had better survival than men. Women were more likely to have adenocarcinoma and stage IA disease, which might account for the better prognosis in women.

Key Words: Gender, Non-small cell lung cancer, Prognosis, Cancer registry.

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Previous studies have reported that lung cancer may represent a somewhat different disease in men and women, and some gender-specific differences have been suggested.[1–6] Gender differences in the distribution of histologic types, stage at presentation, and survival rates have been discussed. Women with lung cancer are more likely to have adenocarcinoma histologically and a better prognosis than men.[2–4,7–13]

Several important prognostic factors have been identified, such as tumor, node, metastasis stage; performance status; gender; age; and histology.[14–16] Among these, the female gender has been repeatedly mentioned as one of the most important factors in both early and advanced lung cancers. Although it has been speculated that women show better survival, the relationship between gender and prognosis has not been clearly demonstrated in a large cohort.

In Japan, the task force committee of the Japanese Joint Committee for Lung Cancer Registration has periodically performed nationwide registry studies on the prognosis and clinicopathologic profiles of lung neoplasms.[14,17] The studies are planned at 5-year intervals to observe changes and trends in clinicopathologic features, such as the prognosis, staging, and histologic distribution, of resected lung cancer patients in Japan. Recently, the committee reported a retrospective registry study that focused on 13,010 cases of lung cancer resected in 1999 after a 5-year follow-up period.[14] This study deals with the retrospective registry for patients with lung cancer resected in 1999.

The aim of this study was to evaluate the characteristics of non-small cell lung cancer (NSCLC) by gender with regard

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to clinicopathologic features and the relationship between gender and prognosis.

PATIENTS AND METHODS

Registry

In 2005, the Japanese Joint Committee for Lung Cancer Registration performed a nationwide retrospective registry study on the prognosis and clinicopathologic profiles of resected lung neoplasms in Japan. Only primary lung neoplasms that had been resected in 1999 at certified teaching hospitals in Japan were considered for the registry, which gave a follow-up period of at least 5 years. The committee received the registries of 13,344 patients from 387 teaching hospitals. The following 32 items were included in the questionnaire: gender, age, smoking status, clinical (c-) T, c-N, c-M, c-stage, preoperative treatment, surgical procedure, extent of lymph node dissection, curability, residual tumor, primary site by lobe, tumor diameter, histology, organ invasion, pathologic (p-) T, p-N, p-M, p-stage, pleural dissemination, intrapulmonary metastasis, pleural cytology, location of nodal metastasis, survival time, recurrence, and cause of death. Recurrent or multiple lung cancers were not included in this registry. Smoking status was recorded as to whether a patient was a smoker within 1 month before the operation. Operative mortality was defined as fatality from any cause within 30 days of the operation or during the same hospitalization. All patients were staged on the basis of the sixth edition of the International Union Against Cancer tumor, node, metastasis classification of the malignant tumor staging system published in 2002,[18] and tumor histology was described according to the World Health Organization classification.[19]

Patients

Sixty-nine patients (0.5%) with incomplete descriptions of their tumor histology and 655 patients (5.0%) with low-grade malignant tumor, nonepithelial tumor histology, or histology of small cell carcinoma were excluded from the study. In addition, 111 patients (0.8%) for whom gender was not given were also excluded from this study. Therefore, this study focused on the remaining 12,509 patients with non-small cell histology (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma).

Statistical Analysis

The χ^2 and Student's t tests were used to evaluate the differences in categorical variables and continuous variables, respectively. The survival time was defined as the time between the date of surgery and the last follow-up date. The survival curves were estimated by the Kaplan-Meier method, and differences in survival were assessed by the log-rank test. Overall survival (OS) was defined as the time between operation and death from any cause, except for cases of a death within 30 days of the operation and during the same hospitalization. Disease-specific survival (DSS) was defined as the time between operation and cancer-related death, where deaths from causes other than lung cancer were considered censored. Multivariate analysis by Cox's proportional hazards ratio model was used to test the significance of prognostic factors including gender, age, smoking status (current smoker versus non-/ex-smoker), surgical procedure, histology, curability, tumor size, p-T status, and p-N status. Significance was defined as a p value less than 0.05.

RESULTS

Clinicopathologic Features

There were 8353 (66.8%) men and 4156 (33.2%) women. The clinicopathologic characteristics of the genders are summarized in Table 1. There were 107 (0.9%), 29 (0.2%), 134 (1.1%), and 181 (1.4%) patients who were missing data regarding operative mode, lymph node dissection, surgical curability, and pathologic stage, respectively. These percentages were within an acceptable range as a registry database.

The mean age at surgical resection for women (65.0 years) was significantly younger than that for men (66.4 years). With regard to smoking status according to histology, the proportion of current smoker was 17.3% for men and 2.4% for women in adenocarcinoma histology ($p < 0.001$). In

TABLE 1. Characteristics of Patients with Resected Non-small Cell Lung Cancer

Characteristics	Men (n = 8353)	Women (n = 4156)	p
Age (yr)			
Mean	66.4 ± 9.4	65.0 ± 10.1	<0.001
Smoking status			
Current smoker	1598 (19.2%)	145 (3.5%)	<0.001
Nonsmoker/ex-smoker	6746 (80.8%)	3985 (96.5%)	
Operative mode			
Pneumonectomy	560 (6.7%)	98 (2.4%)	<0.001
Lobectomy	6750 (81.5%)	3500 (84.6%)	0.226
Segmentectomy/wedge	975 (11.8%)	537 (13.0%)	0.097
Lymph node dissection			
Mediastinohilar	6375 (76.5%)	3101 (74.7%)	0.410
Hilar only/none	1907 (22.9%)	1023 (24.7%)	0.086
Unknown	48 (0.6)	26 (0.6)	0.732
Surgical curability			
Complete	7423 (89.9%)	3734 (90.7%)	0.736
Incomplete	735 (8.9%)	320 (7.8%)	0.052
Unknown	101 (1.2%)	62 (1.5%)	0.199
Operative mortality	222 (2.7%)	31 (0.7%)	<0.001
Histology			
Adenocarcinoma	4498 (53.9%)	3670 (88.3%)	<0.001
Squamous cell carcinoma	3305 (39.6%)	359 (8.6%)	<0.001
Large cell carcinoma	403 (4.8%)	69 (1.7%)	<0.001
Adenosquamous cell carcinoma	145 (1.7%)	58 (1.4%)	0.162
Pathologic stage			
IA	2627 (31.9%)	2105 (51.4%)	<0.001
IB	1912 (23.2%)	694 (16.9%)	<0.001
IIA	255 (3.1%)	105 (2.6%)	0.106
IIB	1074 (13.1%)	242 (5.9%)	<0.001
IIIA	1349 (16.4%)	498 (12.1%)	<0.001
IIIB/IV	1014 (12.3%)	453 (11.1%)	0.070

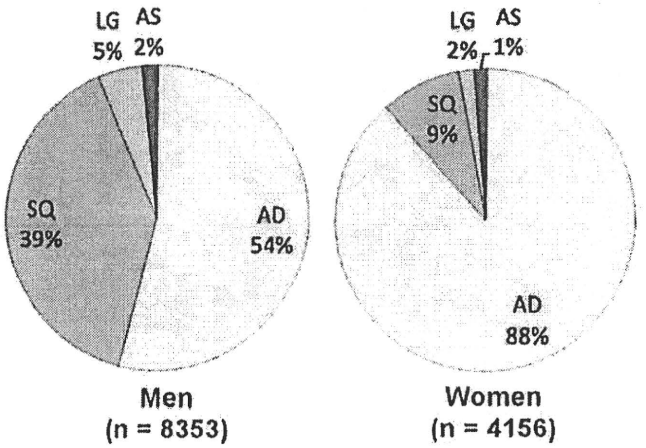

FIGURE 1. Distribution of histologic types between men and women. AD, adenocarcinoma; SQ, squamous cell carcinoma; LG, large cell carcinoma; AS, adenosquamous cell carcinoma.

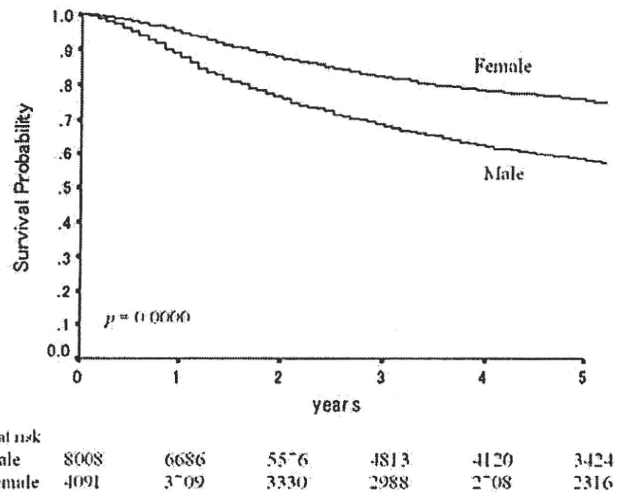

FIGURE 2. Overall survival curves based on gender. The 5-year survival rates of female (n = 4091) and male (n = 8008) patients are 75.6 and 57.9%, respectively. The difference in survival between the genders is significant (p = 0.0000).

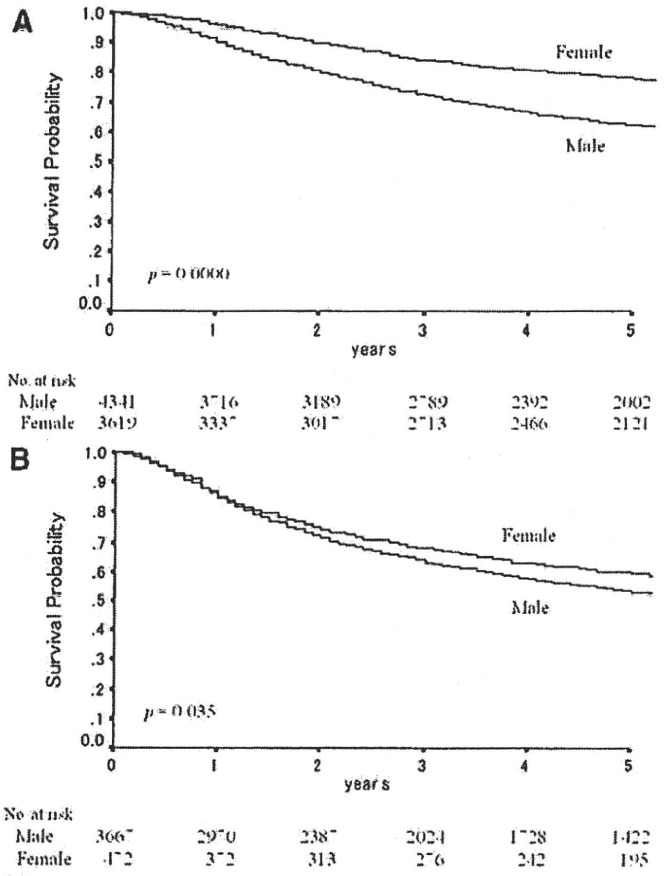

FIGURE 3. Overall survival curves according to gender in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for adenocarcinoma is 61.9% for male patients and 77.7% for female patients. The difference in survival is significant (p = 0.0000). The 5-year survival rate for nonadenocarcinoma is 53.1% for male patients and 59.3% for female patients. The difference in survival is significant (p = 0.035).

nonadenocarcinoma histology, the proportion of current smoker was 21.3% for men and 12.1% for women ($p < 0.001$). In addition, the proportion of current smoker in women also showed significant difference between histologic types (adenocarcinoma versus nonadenocarcinoma) ($p < 0.001$), and the difference between histologic types was also significant in men ($p < 0.001$). Deaths within 30 days of the operation, which were included in operative mortality, were 97 patients (1.2%) for men and 22 (0.5%) for women ($P < 0.001$). Although adenocarcinoma was the most common histologic type in both genders, the distribution of histologic types was significantly different between the genders. The distribution according to histologic type in men and women is shown in Figure 1. Women had significantly more adenocarcinoma ($p < 0.001$) and less squamous cell carcinoma ($p < 0.001$) than men. As for the pathologic stage, women had a significantly higher incidence of stage IA disease than men ($p < 0.001$).

Survival by Gender

The overall 5-year survival rates (5-YSRs) for men and women were 57.9 and 75.6%, respectively. The survival curves are shown in Figure 2. Women had significantly better survival than men (p = 0.0000). According to the histologic type, women had significantly better overall survival (OS) than men with adenocarcinoma (5-YSR, 77.7 versus 61.9%, p = 0.0000). In nonadenocarcinoma, women again had significantly better OS than men (5-YSR, 59.3 versus 53.1%, p = 0.035) (Figure 3). The prognosis between women and men was further studied with regard to histologic type and pathologic stage. In patients with adenocarcinoma histology and pathologic stage I/II disease, women had significantly better OS than men (Figures 4*A* and 5*A*). In contrast, there was no significant OS difference between the genders among

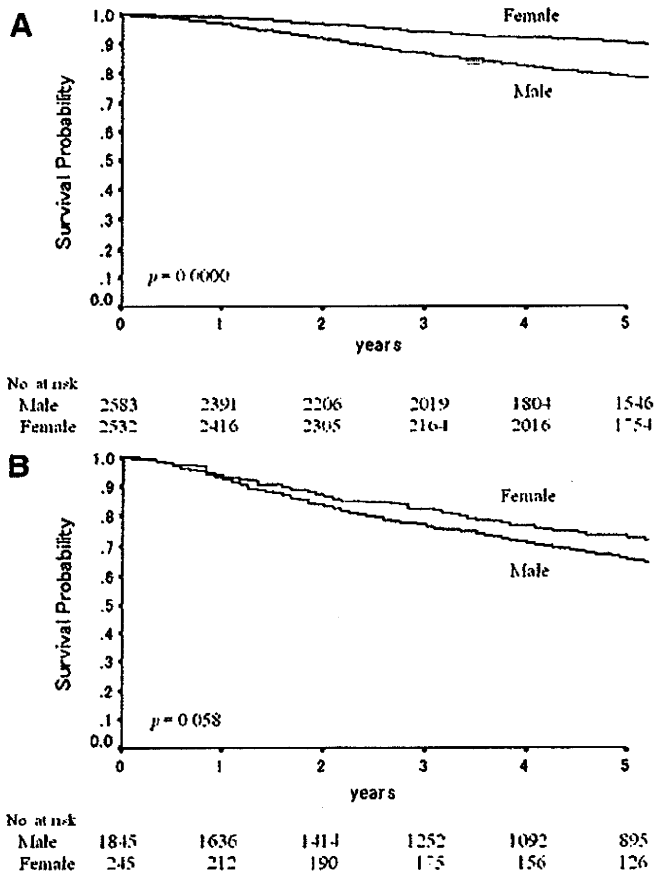

FIGURE 4. Overall survival curves according to gender of pathologic stage I in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for pathologic stage I in adenocarcinoma is 78.6% for male patients and 90.0% for female patients ($p = 0.0000$). The 5-year survival rate for pathologic stage I in nonadenocarcinoma is 65.4% for male patients and 72.8% for female patients ($p = 0.058$).

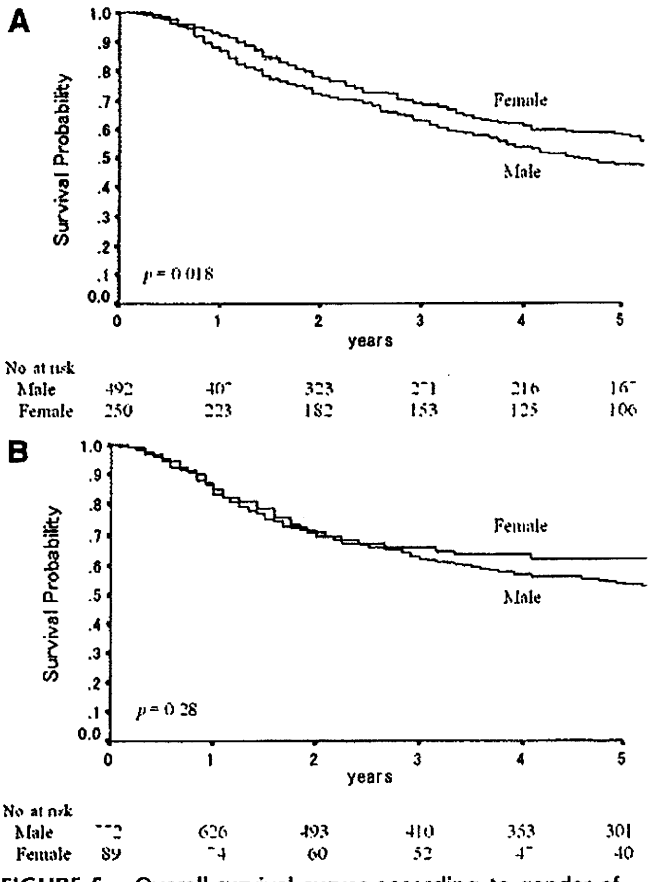

FIGURE 5. Overall survival curves according to gender of pathologic stage II in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for pathologic stage II in adenocarcinoma is 47.5% for male patients and 57.5% for female patients ($p = 0.018$). The 5-year survival rate for pathologic stage II in nonadenocarcinoma is 53.5% for male patients and 61.9% for female patients ($p = 0.28$).

patients with nonadenocarcinoma histology and pathologic stage I/II disease (Figures 4*B* and 5*B*).

Disease-specific 5-YSRs for men and women were 64.9 and 79.2%, respectively (Figure 6). Women had significantly better DSS than men ($p = 0.0000$). According to histologic type, women had significantly better 5-year DSS than men with adenocarcinoma (Figure 7*A*). However, in nonadenocarcinoma, there was no statistical difference in DSS between genders (Figure 7*B*). Regarding histologic type and pathologic typo, the difference between genders in DSS was significant only in patients with adenocarcinoma histology and pathologic stage I disease (Figures 8 and 9).

In a Cox proportional hazards model to predict OS, the following factors persisted as important prognostic factors: gender, age, surgical procedure, histology, curability, tumor size, p-T status, and p-N status (Table 2). Gender had impact on survival with relative risk for women of 0.63 ($p = 0.000$; 95% confidence interval 0.58–0.68). Smoking status was not statistically significant or important determinant of survival, with relative risk for current smoker of 1.00 ($p = 0.94$; 95% confidence interval 0.93–1.09).

DISCUSSION

In this Japanese Lung Cancer Registry Study of 12,509 patients with resected NSCLC, women showed significantly better survival than men after resection. Female gender was one of the statistically positive independent predictors of survival in this registry. This better survival for women was observed regardless of the histologic type (adenocarcinoma or nonadenocarcinoma). Many other studies that have evaluated the effect of gender on the lung cancer prognosis have also suggested that women have a survival advantage, but the reasons for this survival advantage have remained unknown.[3,4,8,11,20] Genetic, metabolic, and hormonal factors have been proposed as potential explanations for the survival benefit experienced by women.[21–23]

The histology of NSCLCs among women was distinctly different from that among men, although adenocarcinoma was the most common histologic type in both genders in this study. Women had so much higher incidence of adenocarcinoma than men. Adenocarcinoma accounted for approximately 90% of resected NSCLC in women, in contrast to only 54% in men. In addition, a large proportion of

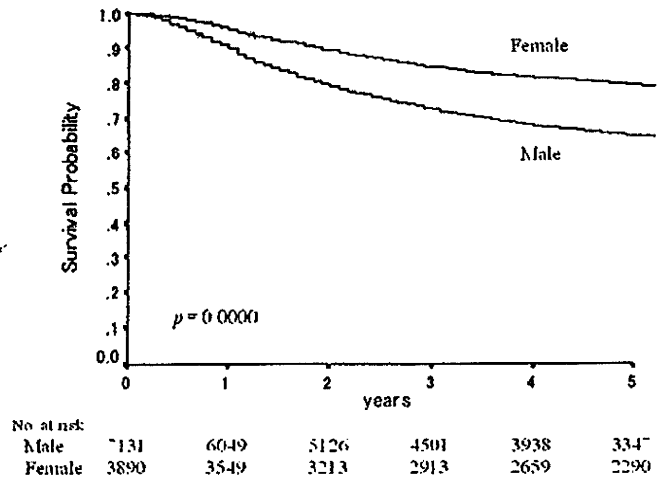

FIGURE 6. Disease-specific survival curves based on gender. The 5-year survival rates of female (n = 3890) and male (n = 7131) patients are 79.2 and 64.9%, respectively. The difference in survival between the genders is significant (p = 0.0000).

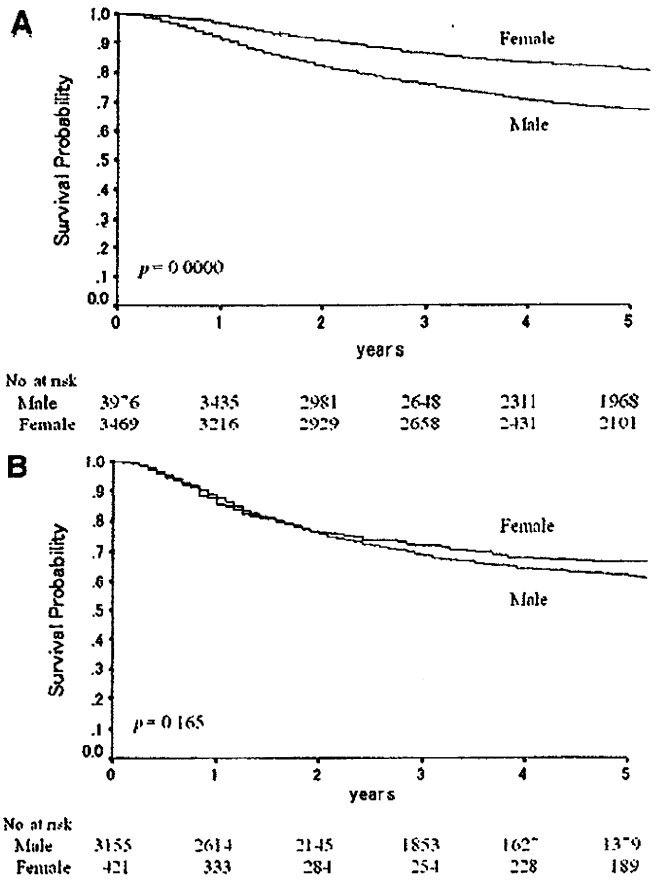

FIGURE 7. Disease-specific survival curves according to gender in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for adenocarcinoma is 67.5% for male patients and 80.8% for female patients. The difference in survival is significant (p = 0.0000). The 5-year survival rate for nonadenocarcinoma is 61.6% for male patients and 66.3% for female patients. The difference in survival is not significant (p = 0.17).

resected NSCLC in females was stage IA disease. In Japan, there have been opportunities of resecting small-sized lung cancers since a computed tomography (CT) screening for lung cancer was introduced in early 1990s. Most of the lung cancers detected by CT screening were likely to be small-sized and slow-growing adenocarcinomas.[24,25] In addition, people with lung cancer detected by CT screening accounted for a large proportion of women.[26] This would be one of the reasons for the increased incidence of early-stage lung cancers among women. In fact, it has been reported that early-stage lung cancers such as bronchioloalveolar carcinoma or adenocarcinoma mixed bronchioloalveolar subtype tend to occur frequently in nonsmoking women.[27,28] These data indicated that the difference in the pathobiologic characteristics of adenocarcinoma between genders should be addressed.

The increased incidence of adenocarcinoma among women may be attributed to several causes, including genetic, biologic, and environmental factors. Genetic polymorphisms and the mutation of specific genes have been examined as possible causes of the predominance of the adenocarcinoma histology in women.[29–31] Epidermal growth factor receptor and *K-ras* gene mutations have been detected more commonly in women than men and have been found mainly in adenocarcinomas of the lung.[29–32] Several reports[33,34] have investigated the relationship between the hormonal effects of estrogen and the development of lung cancer, especially adenocarcinoma, because the obvious biologic differences between men and women are hormonal. These findings in this study and the literature also suggest that the pathway of carcinogenesis might be different between women and men.

On the other hand, we observed that women with adenocarcinoma had a significantly better prognosis in both stage I disease and stage II disease, whereas there was no significant gender difference in nonadenocarcinoma patients with either stage I or stage II. Based on the fact that adenocarcinoma was more common in women and they have better prognosis, adenocarcinoma in women may be supposed to have different pathobiologic behaviors than that in men. The differences in lung cancer and its occurrence between women and men have been found or hypothesized to be related to several factors, such as differences in smoking habits and genetic, biologic, hormonal, and other differences between the genders.[22,33,35,36] Adenocarcinoma has always represented the majority of lung cancer cases among nonsmoking patients.[7,22,23] The association between smoking and lung cancer is much stronger for small cell carcinoma, squamous cell carcinoma, and large cell carcinoma than for adenocarcinoma.[10,37] The proportion of smokers among men is known to be significantly higher than that among women according to several previous reports,[1,38] although we were not able to directly evaluate the effect of potential gender differences in smoking habits because detailed data on tobacco exposure were not recorded in this registry. According to a report by the Health and Welfare Statistics Association in Japan, the proportion of Japanese smokers was 70 to 60% for men,

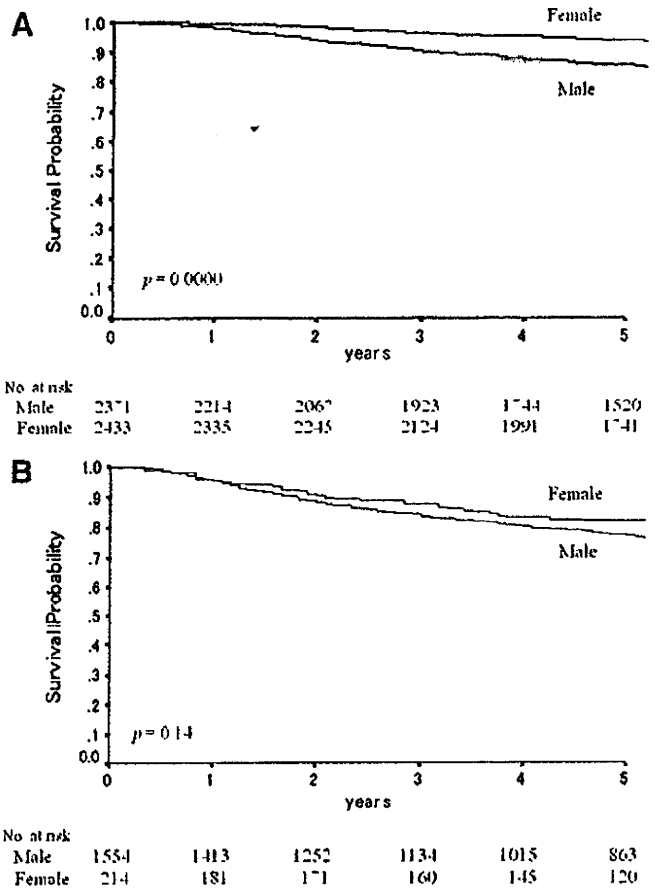

FIGURE 8. Disease-specific survival curves according to gender for pathologic stage I in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for pathologic stage I in adenocarcinoma is 85.3% for male patients and 93.5% for female patients ($p = 0.0000$). The 5-year survival rate for pathologic stage I in nonadenocarcinoma is 77.1% for male patients and 81.9% for female patients ($p = 0.14$).

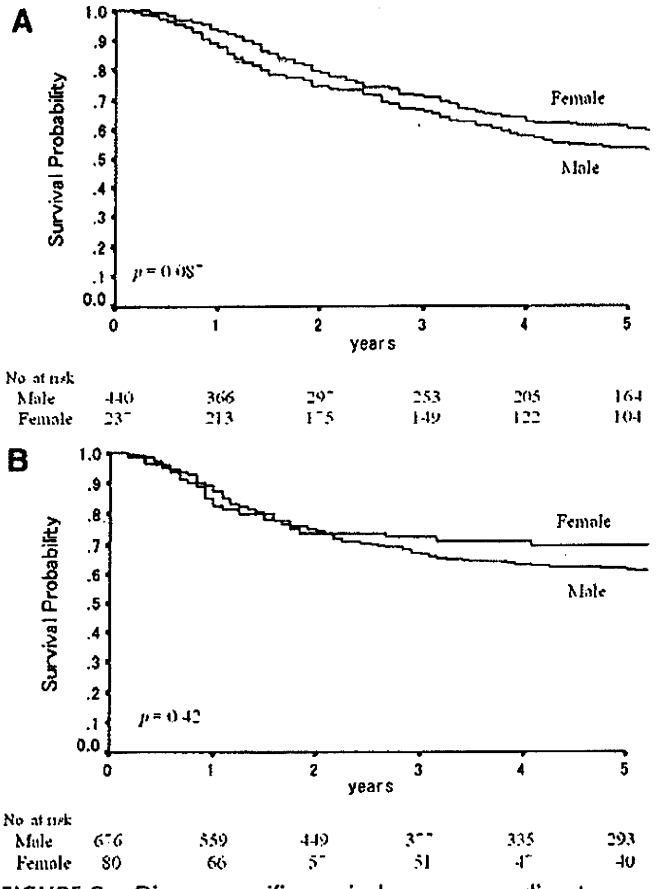

FIGURE 9. Disease-specific survival curves according to gender for pathologic stage II in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for pathologic stage II in adenocarcinoma is 53.4% for male patients and 60.0% for female patients ($p = 0.087$). The 5-year survival rate for pathologic stage II in nonadenocarcinoma is 61.1% for male patients and 69.3% for female patients ($p = 0.42$).

invariable 14% for women, from 1980s to 1990s.[38] The proportion of smokers for men is still higher than that for women, although it has been reducing little by little.[38] Smoking is also closely related to cardiovascular and pulmonary diseases, e.g., ischemic heart disease, cerebrovascular disorder, and pulmonary emphysema.[39] These diseases might lead to noncancerous death before cancer-specific death. Thus, the better prognosis in women among patients with adenocarcinoma might be partially attributed to the differences in the incidence of noncancerous death between genders because women would include fewer smokers than men. In fact, Chang et al.[8] reported that the female-gender advantage in survival for resected NSCLC changed to no survival advantage for females after propensity score matching (variables: age, smoking status, histologic types, and pathologic stages) between males and females. Hanagiri et al.[40] showed that there was no gender difference in cancer-related survival regardless of a significant female-gender advantage in OS for patients with resected lung adenocarcinoma.

In this registry study, according to relationship between prognosis and the combination of histologic type and pathologic stage, women had significantly better DSS than men only in patients with adenocarcinoma histology and pathologic stage I disease. Therefore, at the least, deaths of causes other than lung cancer are likely to affect survival difference between genders except for patients with stage I adenocarcinoma. A significant female-gender advantage in stage I adenocarcinoma persisted in DSS and OS. Stage I adenocarcinoma in women would presumably include many bronchioloalveolar carcinomas, which tend to occur often in nonsmoking women, although histologic subtypes in adenocarcinoma was recorded in this registry.

Although the identification of factors that predispose to operative mortality is beyond the scope of this study, an older age at surgical resection and a higher number of pneumonectomies for men could be related to the higher 30-day mortality among men in this series. The higher operative mortality rate in male patients with lung cancer has been previously reported.[41,42]

TABLE 2. Multivariate Analysis of Overall Survival for Resected Cases of Non-small Cell Lung Cancer: Cox Proportional Hazard Model (n = 12,509)

Variable	RR	95% CI	p
Gender			
Men	1.00		
Women	0.626	0.580–0.675	0.000
Age (yr)			
<50	1.00		
50–70	1.287	1.118–1.482	0.000
>70	1.880	1.630–2.167	0.000
Smoking status			
Non-/ex-smoker	1.00		
Current smoker	1.003	0.926–1.087	0.938
Operative mode			
Pneumonectomy	1.00		
Lobectomy	0.926	0.826–1.038	0.189
Segmentectomy	1.155	0.959–1.391	0.128
Wedge resection	1.469	1.250–1.726	0.000
Surgical curability			
Complete	1.00		
Incomplete	1.630	1.480–1.796	0.000
Histology			
Squamous cell carcinoma	1.00		
Adenocarcinoma	0.938	0.874–1.007	0.076
Large cell carcinoma	1.418	1.237–1.627	0.000
Adenosquamous cell carcinoma	1.647	1.348–2.014	0.000
Tumor size (cm)			
≤1.0	1.00		
1.1–1.5	1.276	1.006–1.620	0.045
1.6–2.0	1.646	1.323–2.049	0.000
2.1–2.5	1.712	1.378–2.128	0.000
2.6–3.0	1.748	1.402–2.178	0.000
3.1–4.0	1.576	1.257–1.975	0.000
4.1–5.0	1.914	1.519–2.412	0.000
5.1–6.0	1.977	1.552–2.520	0.000
≥6.1	2.365	1.869–2.994	0.000
p-T status			
T0	1.00		
T1	0.897	0.602–1.335	0.591
T2	1.475	0.985–2.209	0.059
T3	1.923	1.277–2.895	0.002
T4	2.070	1.378–3.107	0.000
p-N status			
N0	1.00		
N1	1.874	1.716–2.047	0.000
N2	3.039	2.825–3.269	0.000
N3	4.872	3.965–5.986	0.000

RR, relative risk; CI, confidence interval.

In conclusion, we found that women showed significantly better 5-year survival than men after surgical resection of NSCLC. Especially in adenocarcinoma, the survival advantage for women was significant in pathologic stages I and II, whereas in nonadenocarcinoma, this gender difference was not significant in pathologic stage I or II. Although adenocarcinoma is the most common histologic type in both genders, the proportion of adenocarcinoma and stage IA disease in women was much greater than that in men. The incidence of early-stage adenocarcinoma might reasonably account for a better prognosis in women as a whole. Further studies should focus on the identification of differences in the pathobiological nature of early lung adenocarcinoma between women and men.

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ORIGINAL ARTICLE

Long-term outcomes of three-dimensional conformal radiation therapy combined with neoadjuvant hormonal therapy in Japanese patients with locally advanced prostate cancer

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Abstract
Background The outcomes of three-dimensional conformal radiation therapy (3D-CRT) combined with neoadjuvant hormonal therapy (NAHT) in Japanese patients with locally advanced prostate cancer who initiated salvage hormonal therapy (SHT) at a relatively early phase were evaluated.
Methods Between April 1998 and April 2003, 70 Japanese patients with T3N0M0 prostate cancer who received radical 3D-CRT treatment were evaluated. The median age, initial prostate-specific antigen (PSA) level, and duration of NAHT were 73 years old, 26.3 ng/ml, and 4 months, respectively. Seventy grays were given in 35 fractions that were confined to the prostate and seminal vesicles. Adjuvant hormonal therapy was not administered after 3D-CRT in any of the cases.
Results The median follow-up period was 64.9 months. The median PSA value at the time of initiation of SHT was 5.0 ng/ml (range 0.1–21.6 ng/ml). Overall, disease-specific, PSA failure-free (based on the Phoenix definition) and SHT-free survival rates at 5 years were 90.3% (95% CI 86.5–94.0), 96.5% (94.0–98.9), 60.5% (48.2–72.7), and 63.5% (57.2–69.8), respectively. Therefore, two-thirds of the patients were still hormone-free at 5 years.
Conclusions PSA control rates in our series of Japanese patients with stage T3N0M0 prostate cancer treated with the standard dose of 3D-CRT combined with NAHT seemed higher than expected. This approach involving 3D-CRT combined with NAHT with the initiation of SHT at PSA values of around 5 ng/ml may be one option for Japanese patients with locally advanced prostate cancer, although further prospective study is required to confirm the validity.

Keywords Prostate cancer · Neoadjuvant hormonal therapy · Three-dimensional conformal radiation therapy · PSA failure · Salvage hormonal therapy

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Introduction

Prostate cancer is the most common form of cancer in men in the USA, with 218,890 cases diagnosed and 27,050 deaths annually [1]. This disease ranks first in morbidity rate and second in mortality rate among males in the USA [2]. On the other hand, among Japanese males, prostate cancer ranks sixth and eighth in morbidity and mortality rates, respectively [3, 4]. However, both rates have been increasing rapidly in recent years [5, 6].

Moreover, in Europe and the USA, most patients newly diagnosed with prostate cancer are at the T1-2N0M0 stage. In contrast, a significant number of locally advanced cases are still encountered in Japan, accounting for about 35% of

all prostate cancer cases in Japan in 2000 [6]. Therefore, research into better treatment for stage T3-4N0M0 prostate cancer has immense significance for Japanese males in particular.

As the outcomes of radical prostatectomy in patients with locally advanced (stage T3N0M0) prostate cancer are considerably inferior to those for patients with stage T1-2N0M0 disease [7], external beam radiotherapy (EBRT) combined with hormonal therapy (HT) is recommended as the first choice for treating patients with locally advanced (stage T3N0M0) prostate cancer [8, 9]. In addition, a combination of long-term adjuvant hormonal therapy (AHT) with EBRT is recommended based on the results of a randomized trial [10–12].

However, it has not been proven that the findings described above can be also applied to the Japanese (Asian) population. This is because Japanese urologists generally tend to readily administer HT, even after giving definitive treatment, and the effects of HT may differ in the Japanese population [6, 13]. In addition, there have been very few reports regarding the outcome of EBRT when it is not used in combination with long-term AHT in cases of prostate cancer among Japanese male. At Kyoto University Hospital, we applied EBRT via the three-dimensional conformal radiotherapy (3D-CRT) technique in conjunction with neoadjuvant hormonal therapy (NAHT) in patients with stage T3N0M0 prostate cancer without any AHT. We reported the outcomes for patients treated with this strategy involving strict adherence to our protocol of 3 months of NAHT [14]. However, a considerable number of the patients treated at our institution were referred from other institutions and had already been administered HT for more than 3 months.

Therefore, in the present study, a retrospective evaluation of outcomes of patients treated consecutively with 3D-CRT combined with NAHT for stage T3N0M0 prostate cancer at a single institution was performed to demonstrate the prognostic outcomes of Japanese patients not given AHT.

Patients and methods

Patient characteristics

Between April 1998 and April 2003, 177 Japanese men with T1-4N0M0 (according to the classification of the International Union Against Cancer: UICC '97) prostate cancer were treated consecutively with EBRT at our institution. Among them, 104 patients were staged as T3N0M0, and there was no T4N0M0 case. These 104 patients consisted of 10 patients with hormone-refractory prostate cancer, 6 patients who received long-term (>30 months) intermittent HT, and 15 who elected for the intensity-modulated radiation therapy (IMRT) protocol conducted as a pilot or a phase I/II dose escalation study. In addition, 1 patient was treated with 3D-CRT alone and 2 patients elected for whole-pelvis irradiation (Table 1). Therefore, 70 patients who were treated with short-term NAHT followed by localized 3D-CRT with definitive intent were analyzed in this study.

The median age of the 70 patients was 73 years (range 48–80) at the beginning of RT. T stages (UICC '97) were distributed as follows: 54 cases with T3a and 16 with T3b. T-stage was classified based on the findings of digital rectal examination, transrectal ultrasound, or magnetic resonance imaging (MRI). However, MRI was applied to less than one-third of this cohort of patients. Thus, for the patients who were referred after initiating HT, we adopted the staging assessed by the urologist at the initial visit if validation could not be achieved with the available imaging and clinical data. With respect to the Gleason scores (GS), 10, 32, and 27 cases had grades of ≤6, 7, and ≥8, respectively. The GS of the remaining patient was unknown. Initial prostate-specific antigen (PSA) levels ranged from 3.7 to 430 ng/ml, with median and average values of 26.3 and 54.7, respectively.

Table 1 Patient characteristics and treatment parameters

Number of cases	70
Age (years)	48–80 (median 73)
T stage (UICC'97)	
T3a	54
T3b	16
Gleason score	
≤6	10
7	32
≥8	27
Unknown	1
Initial PSA value (ng/ml)	3.7–430 (median 26.2, average 54.7)
Follow-up period (months)	8.0–117.7 (median 65.7)
NAHT period (months)	3–16 (median 4)
NAHT regimen	
MAB	61
LH-RH analog alone	9
RT dose (Gy)	
60	1
64	3
66	1
69.4	1
70	64
RT method	
4-port → arcs	65
4-port → 4-port	1
Arcs → arcs	4

Hormonal therapy

Before initiating 3D-CRT, NAHT consisting of maximum androgen blockade for 3 months was planned. However, there were variations in the duration and content of HT because considerable numbers of patients were referred from other institutions after having started HT. Therefore, the duration of NAHT ranged from 3 to 16 months, with a median duration of 4 months. Among the 70 patients included in this study, 61 patients received maximal androgen blockade (MAB), LH-RH analog (goserelin acetate or leuprorelin acetate), plus anti-androgen (flutamide, bicalutamide, or chlormadinone acetate). Another 9 patients were administered LH-RH analog alone because of liver dysfunction. No AHT was given to any patient after the completion of 3D-CRT until PSA failure or clinical failure occurred.

Radiation therapy

Planning CT scans were obtained using a CT simulator (CTS-20; Shimadzu, Kyoto, Japan) with a slice thickness of 5 mm, without a gap from the iliac crest to 8 cm below the ischial tuberosity. Patients were placed in the supine position without any fixation devices. They were instructed to void the bladder and rectum about 1–1.5 h before CT simulation, according to their individual urinary conditions. Target delineations and treatment planning were performed with CadPlan (ver. 6.2.7) or Eclipse (ver. 7.1.35) (Varian Medical Systems, Palo Alto, CA). The 15-MV photon beams of a Clinac 2100C or 2300 C/D (Varian Medical Systems). The final dose distributions for all plans were calculated using a pencil beam convolution algorithm with a calculation grid resolution of 2.5 × 2.5 mm, in which the modified Batho heterogeneity correction was applied.

The clinical target volume (CTV) was defined as the prostate and seminal vesicles. No planning target volume (PTV) was used in this protocol. Instead, the edges of the multileaf collimator (MLC) were fitted directly to the CTV with designated margins as described below. A total irradiation dose of 46 Gy in 23 fractions was initially given by the 4-field box technique with MLC conformation to the CTV, followed by an additional 24 Gy in 12 fractions with the dynamic arc conformal technique [14, 15]. In 4-field irradiation, the edges of the MLC were fitted directly to the CTV with a 15-mm margin in all directions based on the beam's eye view of each field. If part of the posterior rectal wall was included within the irradiated field in the lateral opposing fields, the MLC position was adjusted manually to completely shield the posterior rectal wall from the irradiated volume of the bilateral fields (Fig. 1). In dynamic arc conformal radiotherapy, two lateral arcs with

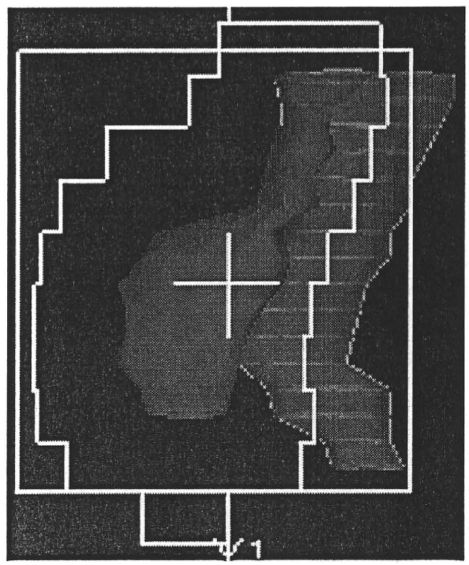

Fig. 1 An example of the lateral port (from left to right) of the multileaf collimator (MLC)-shaped 4-port technique is shown. The clinical target volume (CTV) was defined as the prostate and seminal vesicles. A 15-mm MLC margin was added to the CTV. The position of the MLC was adjusted manually to prevent irradiation of the posterior rectal wall by the bilateral lateral ports

100° of rotation (from 36° to 136°, and 226° to 326°) were used with dynamic conformal fitting of the MLC to the CTV with a 7-mm margin. This technique enables continuous beam delivery while the MLC position can be changed dynamically to conform to the target as the gantry rotates. The margin from the superior and inferior jaw to the edge of the CTV was 13 mm.

The prescribed dose was 70 Gy in 35 fractions at the center of the CTV, which was the isocenter of the fields (Fig. 2). The total dose was reduced to 4–10 Gy in patients with at least one of several possible risk factors, including diabetes mellitus, collagen disease, etc.

Patient follow-up and salvage hormonal therapy

After the completion of EBRT, patients were followed up without the administration of AHT. The PSA value was examined every 2–4 months. Salvage HT (SHT) was, in principle, initiated when the PSA value exceeded 4 ng/ml after PSA failure, or when any clinical failures were detected.

Outcome evaluation and statistical analyses

The overall survival (OAS), disease-specific survival (DSS), PSA failure-free survival (PFS), and SHT-free survival (SHFS) rates were calculated by Kaplan–Meier estimation from the initiation date of EBRT [16]. The PFS rates were evaluated based on both the modified ASTRO definition and the Phoenix definition [17, 18]. Because

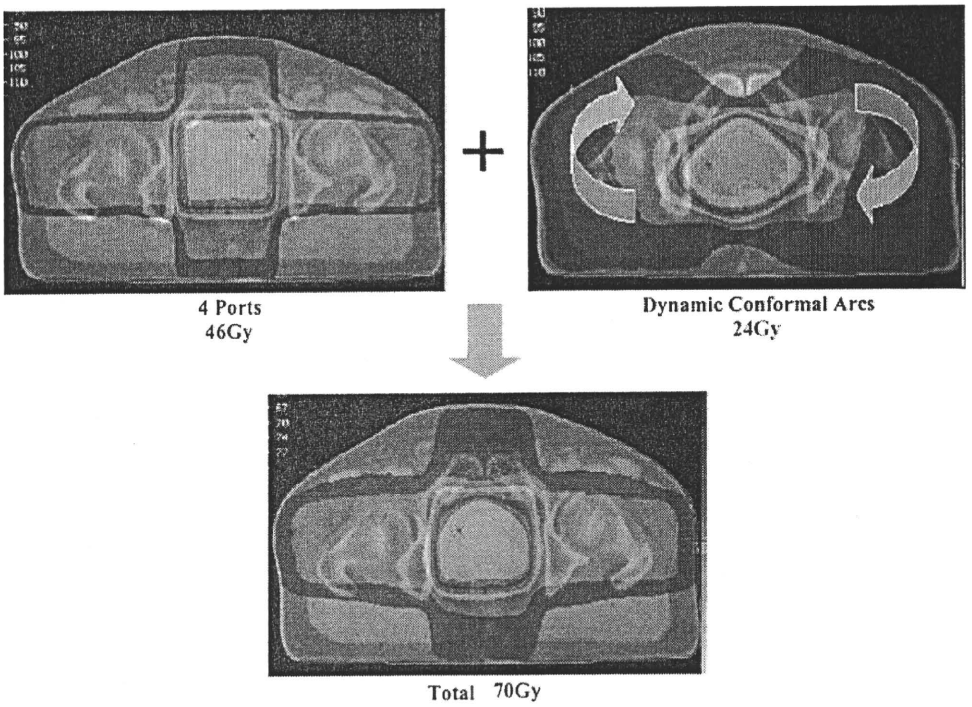

Fig. 2 An example of the dose distribution is shown. A total of 70 Gy was delivered in 35 fractions to the prostate and seminal vesicles combined using the multileaf collimator (MLC)-shaped 4-port technique (46 Gy/23 fractions) and the dynamic arc conformal technique (24 Gy/12 fractions)

NAHT was initiated, we applied the modified ASTRO definition; (1) fluctuations of PSA below 0.5 ng/ml were not counted, (2) elevations of 0.1 ng/ml or more were counted as significant increases. The statistical significance of a difference in survival was estimated by the logrank test. All statistical analyses were performed using JMP (version 5) (SAS Institute Inc., Cary, NC, USA).

Results

The median and average PSA values at the initiation of radiotherapy were 0.3 and 0.8 ng/ml, respectively (range 0.02–4.7 ng/ml). The prescribed dose of 70 Gy was delivered to 65 patients. However, it was reduced to 60–66 Gy in the remaining 5 patients because of diabetes mellitus ($n = 5$) or severe acute adverse urinary effects ($n = 1$).

Sixty-seven patients were treated with MLC-shaped 4-field ports followed by two arcs of the dynamic arc conformal technique. However, one patient was treated with MLC-shaped 4-field ports alone, and two patients were irradiated with dynamic conformal arcs alone.

The follow-up periods ranged from 8.0 to 117.7 months, with a median value of 64.9 months.

The 5-year PFS based on the modified ASTRO definition and the Phoenix definition were 53.5% (95% CI 40.9–66.0) and 60.5% (95% CI 48.2–72.7), respectively (Fig. 3). The 5-year OAS and DSS were 90.4% (95% CI 83.2–97.7) and 96.5% (95% CI 91.7–100.0), respectively (Fig. 4).

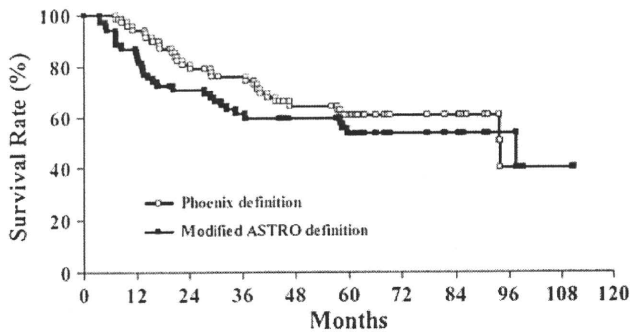

Fig. 3 Kaplan–Meier estimate of prostate-specific antigen failure-free survival (PFS) rate based on the modified ASTRO definition and the Phoenix definition. The 5-year PFS rates were 53.5% (95% CI 66.0–40.9%) and 60.5% (95% CI 72.7–48.2%) for modified ASTRO and Phoenix definitions, respectively

The 5-year SHFS rate was 63.0% (95% CI 50.7–75.2) (Fig. 5). PSA values at the time of initiation of SHT were 0.1–21.6 ng/ml, with a median value of 5.0 ng/ml. The choice of the regimen of salvage hormone therapy employed was left in the hands of the physician in charge.

To date, clinical failures consisting of bone metastases have occurred in 2 patients. With respect to the toxicity, no patient had grade 3 or higher acute complications (CTCAE ver. 3.0), and 8 patients had grade 2 or higher late complications (RTOG late-toxicity criteria). Five patients developed grade 2 rectal bleeding and required steroid suppository and/or hyperbaric oxygenation therapy (HBO). One patient developed grade 3 rectal bleeding and required laser coagulation. Two cases had episodes of macrohematuria, and 1 of

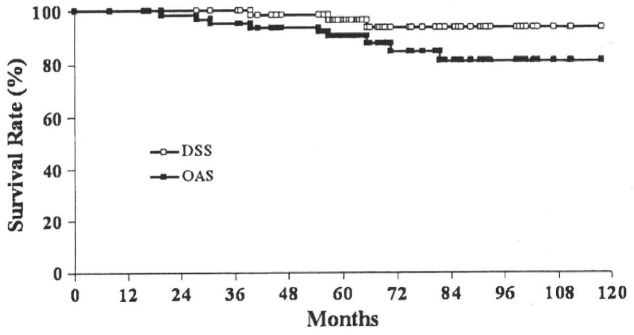

Fig. 4 Kaplan–Meier estimates of overall survival (OAS) rate and disease-specific survival (DSS) rate in all patients. The 5-year OAS and the 5-year DSS were 90.4% (95% CI 97.7–83.2) and 96.5% (100.0–91.7), respectively

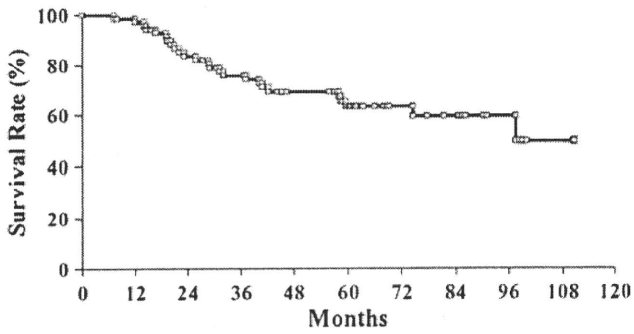

Fig. 5 Kaplan–Meier estimate of the salvage hormonal therapy (SHT)-free survival (SHFS) rate. The 5-year SHFS was 63.0% (95% CI 75.2–50.7). The median prostate-specific antigen (PSA) value at the time of the initiation of SHT was 5.0 ng/ml (range 0.1–21.6 ng/ml)

these 2 patients also developed urethral stricture, which was managed successfully by bougienage.

Discussion

There have been many reports regarding the outcomes of EBRT in patients with locally advanced prostate cancer, mainly from Western countries [8, 10, 11, 19–23]. In these studies, long-term PFS was reported to be around 30% [8, 10, 11, 19–21], although it was never acceptably high when the patients were treated with EBRT alone.

On the other hand, in Japan, surgical operation combined with AHT or permanent HT alone has been widely adopted for patients with T3N0M0 prostate cancer. Therefore, there have been few reports of the results of EBRT alone or EBRT combined with NAHT for T3N0M0 prostate cancer, although some results of EBRT combined with long-term AHT were reported [24, 25]. Therefore, this is one of only a few reports regarding EBRT not combined with long-term AHT in Japanese (Asian) patients with T3N0M0 prostate cancer.

In this study, both PFS and the frequency of treatment-related complications were at least comparable to those reported in other institutions. With respect to the PFS in the present study, it seemed rather higher than expected from the literature reported from Western countries. These observations confirmed that EBRT is an effective treatment method for Japanese men with locally advanced prostate cancer. In our series, about two-thirds of the patients remained hormone-free at 5 years.

In a randomized trial that compared EBRT alone and EBRT plus long-term AHT, a significant survival benefit was observed in the AHT arm [10, 11]. In addition, long-term (3 years) AHT was better than short-term (6 months) AHT for high-risk patients with prostate cancer in terms of survival [12]. Therefore, EBRT combined with long-term HT is currently considered the standard treatment strategy for local advanced prostate cancer [26], although short-term NA-HT is still an option for this patient group in Prostate PDQ® [27].

Our approach was different from the standard approach because the protocol was designed before the publication of the abovementioned trials reporting the survival benefits of adding long-term HT. However, we are still using this approach because about two-thirds of our patients remained hormone-free at 5 years, while both OAS and DSS seemed excellent compared to those in similar studies conducted in Western countries, even though no AHT was administered. In fact, the 5-year OAS rate is currently almost comparable to the expected survival rate of age-matched Japanese men calculated from the life table for Japanese men published by the Japanese Ministry of Health, Labor, and Welfare [28].

A number of explanations for our observations are possible. First, a combination of NAHT with EBRT was applied in our series. NAHT, if combined with EBRT, can also improve PFS and DSS (OAS) compared to EBRT alone [8, 22, 29–32]. In fact, RTOG 9202, in which EBRT combined with NAHT and 2 years of AHT was compared with EBRT plus NAHT alone, resulted in no significant impact on the OAS of adding AHT to the original patient group (45% of the patients were T2c stage), although a survival benefit was observed in a subset analysis for the high-risk group of patients with GS $\geq$ 8 [21].

Another possibility is the timing of the initiation of SHT after PSA or clinical failure. Shipley et al. suggested that delayed initiation of SHT would result in a poorer survival outcome. They reported that the prognoses of patients who started SHT when their PSA values were less than 20 were superior to those of patients in whom SHT was initiated at PSA $\geq$ 20 or those who started HT after the detection of clinical failure [33]. In the present study, SHT was started when the PSA value exceeded 4 ng/ml (median value

5.0 ng/ml), and this earlier initiation of SHT may have contributed to the improved prognosis.

The third possibility is that there may be ethnic differences in sensitivity to HT between Western and Asian populations. A retrospective comparison of Japanese Hawaiian and white patients with prostate cancer who were treated with HT alone with respect to the rate of tumor response and survival suggested that Japanese patients with prostate cancer would probably be more sensitive to the treatment than white patients, resulting in a better survival rate [13].

Therefore, our study suggested that Japanese patients with locally advanced prostate cancer can be appropriately managed with EBRT combined with NAHT if SHT is initiated at around 5 ng/ml. However, a longer follow-up is needed to draw conclusions regarding survivals, and the adequacy of this approach should be validated by a prospective randomized trial.

Fortunately, with respect to Japanese patients with locally advanced prostate cancer, a randomized controlled trial is currently underway involving treatment with 72 Gy EBRT by 3D-CRT combined with 6 months of NAHT followed by randomization of continuous androgen ablation (arm 1) or intermittent androgen ablation (arm 2) [34]. In this study, the initiation of HT in the intermittent HT group (arm 2) is scheduled for a PSA level of $\geq$5 ng/ml (initially $\geq$10 ng/ml). Therefore, this study is expected to compare the adequacy of short-term AHT with early initiation of SHT with that of long-term AHT in Japanese (Asian) patients with locally advanced prostate cancer.

Conclusions

The outcomes of three-dimensional conformal radiation therapy combined with NAHT for Japanese patients with T3N0M0 prostate cancer suggested that OAS may be comparable to the expected survival rate if SHT is initiated earlier (>4 ng/ml), and that two-thirds of cases are free from HT at 5 years. This should be validated by a future prospective randomized trial in the near future, as well as by the outcome of an ongoing prospective randomized trial comparing the adequacies of permanent and intermittent AHT after EBRT with NAHT for Japanese patients with locally advanced prostate cancer.

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Conflict of interest statement Authors have no conflicts of interest.

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BRACHYTHERAPY

High–dose rate brachytherapy alone in postoperative soft tissue sarcomas with close or positive margins

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ABSTRACT

PURPOSE: In the management of soft tissue sarcomas, perioperative radiation therapy has been used to reduce the risk of local recurrence after resection. However, a significance of postoperative high–dose rate brachytherapy (HDRBT) remains to be studied. Retrospective analysis was performed to elucidate the role of postoperative HDRBT.

METHODS AND MATERIALS: Twenty-five patients with 26 soft tissue sarcoma lesions underwent postoperative HDRBT using ^{192}Ir remote afterloader without external beam radiation therapy. Ninety-two percent of the lesions were Grade 2 or 3 malignancies, and 50% were resected with positive surgical margins. The remaining 50% had very close margins. Fourteen lesions were treated for local recurrences after previous resections. Applicators of HDRBT were placed during the operation to include only the tumor bed excluding surgical scars. Applied dose was mainly 36 Gy/6 fractions/3 d b.i.d.

RESULTS: Five-year local recurrence-free survival was 78.2% in all the 26 lesions. Recurrences were not seen within the treated volume of HDRBT. Two groups were defined according to the marginal status and number of previous operations. Group 1 was the lesions with a positive margin and foregoing resections. The remaining lesions were classified as Group 2. Five-year local recurrence-free survival was 43.8% and 93.3% in Group 1 and Group 2, respectively with a statistically significant difference ($p = 0.004$).

CONCLUSIONS: Postoperative HDRBT was effective in controlling local lesions; but in Group 1 lesions, addition of a wide field external beam radiation therapy seems to be necessary to improve the local control rate.

Keywords: High–dose rate brachytherapy; Soft tissue sarcoma; Postoperative radiation

Introduction

In the management of soft tissue sarcomas (STSs), surgical resection is the mainstay of treatment. However, local recurrence is seen frequently, especially in the patients with positive surgical margins, a large tumor, and/or recurrence after foregoing surgery (1, 2). Post- or preoperative radiation therapy has been demonstrated to be effective in reducing the risk of local recurrence (2–4). Furthermore, the combination of surgery and perioperative radiation therapy has changed the management policy of the STSs from a mutilating radical amputation to limb-sparing therapy. External beam radiation therapy (EBRT) is the most frequently used method of radiation therapy, whereas postoperative radiation therapy using low–dose rate brachytherapy (LDRBT) has been reported to be also effective in lowering the local recurrence rate (3, 5). In contrast, postoperative high–dose rate brachytherapy (HDRBT) of STS has been published only sporadically and its clinical significance in the management of STSs remains to be studied (6–10). In National Cancer Center Hospital, HDRBT has been used without EBRT in the postoperative radiation therapy of patients with STSs, whose

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removal seemed to result in a resection with positive or close margins. In this study, the role and significance of postoperative HDRBT alone in the management of STS is analyzed retrospectively.

Methods and materials

From 1995 to 2008, 25 patients with 26 STS lesions underwent postoperative HDRBT alone in National Cancer Center Hospital. There were 10 men and 15 women. In a male patient with malignant fibrous histiocytoma, the lesion was managed with operation and postoperative HDRBT and the tumor recurred proximal to the original site. The recurred tumor was resected and postoperative HDRBT was administered repeatedly (Table 1). Median age was 60.7 years ranging from 9 to 76 years. Primary sites of the tumors were upper extremity with 12 lesions and lower extremity with 11 lesions. Primary truncal STS was seen in three lesions. As for pathology, malignant fibrous histiocytoma was most frequently seen in 12 lesions followed by leiomyosarcoma in three lesions. Eighty-eight percent of lesions were diagnosed as Grade 2 or 3 in three-tiered grade classification. Surgical margins were microscopically positive for sarcoma cells in 13 lesions; whereas in 13 lesions, resection margins were very close (less than 5 mm) to the tumor because vicinity of the tumor to the functionally important structures, such as major neurovascular bundles, made it difficult to attain adequate surgical margins. The maximal tumor size in the pathologic specimen was 9 cm in a mean with a range between 1.2 cm and 22 cm. Included in the present study were also the STSs, which recurred after previous surgeries. Fourteen lesions were treated by resections and HDRBTs for recurrences after the previous surgeries. Number of the foregoing surgeries ranged from one to eight.

Table 1
Age and sex of the 25 patients and characteristics of the 26 lesions undergoing postoperative high–dose rate brachytherapy for soft tissue sarcomas

Characteristics	Number
Median age (y)	60.7 (range, 9–76)
Sex	
Male:female	11:15
Primary Site	
Upper extremity	12
Lower extremity	11
Trunk	3
Histopathology	
Malignant fibrous histiocytoma	12
Leiomyosarcoma	3
Synovial sarcoma	3
Liposarcoma	2
Rhabdomyosarcoma	2
Others	4
Malignant grade	
1	2
2	9
3	15
Tumor size	
Mean	9 cm (range, 1.2–22)
<5 cm	9
>5 cm	17
Number of previous operations	
0	12
>1	14
Status of surgical margin	
Positive	13
Negative	13
Chemotherapy	
Yes	12
No	14

Indication of the postoperative HDRBT was determined preoperatively by a joint meeting of orthopedic surgeons and radiation oncologists. Postoperative HDRBT was used to preserve major neurovascular bundles or major muscles, which are indispensable to maintain the functional integrity of extremities. During the operation, resection margins close to or contaminated by tumor were confirmed by both orthopedic surgeons and radiation oncologists. Surgical clips were placed to delineate the tumor bed as well as the resection margins very close to the lesion. The flexible applicator tubes of HDRBT were placed to cover the tumor bed with 1–2 cm margins in a parallel fashion with 1–1.5 cm intervals between the tubes. Applicator tubes have a closed end and were sutured to the tumor bed. The open ends of tubes were pulled through the skin and connected to the remote afterloading machine. Muscular or adipose tissue flaps of about 5 mm thickness were used to cover major nerve and/or vascular bundles to avoid direct contact of the applicators. The tubes were removed after completion of the HDRBT. Radiation therapy planning was performed by Plato (version 14.3.7; Nucletron, Veenendaal, The Netherlands). The coordinates of the tube applicators were digitized using orthogonal x-rays and/or CT images. The dwell positions of HDRBT source were located to cover tumor bed encircled by the surgical clips. No special efforts were exerted to include all the scar and drainage sites. Geometric optimization was used to calculate dwell times with a reference poinof 5 mm lateral to the midportion of the central tube applicator. For HDRBT, ^{192}Ir afterloading machine was used (microSelectron HDR; Nucletron, Veenendaal, The Netherlands). All the lesions but one were irradiated with a fractional dose of 6 Gy, and the remaining one was treated by 4.5 Gy because neighboring nerve could not be adequately protected by the flap. The HDRBT was done b.i.d. with an interval between the fractions of at least 6 h. Six fractions were administered in all but one lesion, which was treated with four fractions because of the accidental early slip out of the applicators. In 24 lesions, applied dose was 36 Gy, 30 Gy, and 27 Gy each in one lesion (Table 2). Interval