metastases, multiple lymph node metastases, poor performance status (PS), and non-squamous cell carcinoma (23-29). According to some studies, the results of surgery combined with radiotherapy or radiotherapy alone are relatively good in stage IVb cervical carcinoma patients with para-aortic lymph node metastases alone (30-33). However, chemotherapy for stage IVb patients with cervical/mediastinal lymph node or main organ metastases, without surgery and radiotherapy, has been reported to have only slight effect.

In this study, we retrospectively investigated the clinicopathological features of stage IVb cervical carcinoma, and evaluated the efficacy of chemotherapy for this stage of cancer.

Patients and methods

Patients with stage IVb cervical carcinoma were diagnosed and treated in the National Cancer Center Hospital between April 1997 and March 2006. Stage was evaluated according to the FIGO staging. We rectrospectively reviewed the medical chart of these patients.

Treatment. Therapeutic strategies were selected for individual patients. For surgery, total hysterectomy (radical hysterectomy in some patients) and bilateral salpingo-oophorectomy were performed. Pelvic and/or para-aortic lymphadenctomy were performed in some patients. For radiotherapy, the area of external irradiation was established as the entire pelvic region from the closed pore to the L4/5 lumbar vertebrae, with a radiation dose of 2 Gy per treatment (total dose, 50-60 Gy). When the cumulative dose reached 20-30 Gy, external irradiation was combined with high-dose intra-cavity irradiation, with a central shield, at a radiation dose of 5 Gy (total dose, 20-25 Gy). When imaging findings suggested para-aortic lymph node metastases, biopsy was performed. After a definitive diagnosis of metastases was made, the irradiation field was extended to include the para-aortic node. For chemotherapy, eligible patients participated in a phase II clinical study with an in-house protocol that we previously reported, including paclitaxel (PTX)/carboplatin (CBDCA) therapy (Kitagawa R, *et al*, Proc ASCO 22: abs. 5048, 2004) (PTX, 175 mg/m^2, CBDCA AUC5, day 1, every 3 weeks for 6 cycles), and carboplatin (CBDCA)/irinotecan (CPT) therapy (Hori S, *et al*, Proc ASCO 21: abs. 835, 2002) (CBDCA AUC5, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles). For patients with PS of 3, weekly PTX/CBDCA therapy (PTX 80 mg/m^2, CBDCA AUC2, continuous administration for 20 weeks) was administered. In 1 patient with small cell carcinoma, cisplatin (CDDP)/CPT therapy (CDDP, 60 mg/m^2, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles) was administered as postoperative adjuvant therapy.

Best supportive care (BSC) was defined as treatment targeting the relief of symptoms without surgery, radiotherapy or chemotherapy, as described above.

Evaluation. Pretreatment clinical evaluation was repeated before each treatment cycle with the exception of radiography or CT/MRI imaging, which was repeated at least every other treatment cycle. Treatment was continued until disease progression or adverse effects precluded further administration. The response to treatment, in terms of the best response achieved in a given patient, was assessed using standard clinical criteria. A complete response (CR) was defined as the disappearance of all gross evidence of disease for at least 4 weeks. A partial response (PR) was defined as a >50% reduction in the product of perpendicular diameters obtained from the measurement of each lesion, sustained for at least 4 weeks. Progressive disease (PD) was defined as a >50% increase in the product of perpendicular diameters of any lesion documented within 2 months of study entry or the appearance of any new lesion within 8 weeks of study entry. Stable disease (SD) was any condition not meeting any of the above three criteria. Overall survival was measured as the observed length of life from protocol entry to death or (for living patients) date of last contact. Progression-free survival was measured from the date of initiation of protocol to the first progression or death, or to the date of last contact for patients who were alive and progression-free.

Persistent disease was defined as carcinoma at a pelvic site known to be previously involved within 6 months of staging. Recurrent disease was classified as a new tumor in the extrapelvic area or pelvic disease >6 months after staging in a location previously tumor-free. Persistent or recurrent disease was documented by surgical exploration, biopsy or progression on imaging studies. The time of recurrence or death was calculated from the date of original staging. The end of the follow-up period was March 2006.

Statistical analysis. Statistical analysis was performed using SPSS. The impact of clinical and pathologic risk factors on survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using Cox's proportional hazard model. P-values <0.05 were considered significant.

Results

Thirty-six patients were treated between April 1997 and March 2006. Table I shows the patient characteristics. The median age was 54 years. In 34 patients, PS was almost 0, 1 or 2. In the remaining 2 patients, PS was 3. As initial treatment, surgery was performed in 4 patients, radiotherapy in 17, and chemotherapy in 13. BSC was performed in two patients who did not wish to receive aggressive treatment. Histopathologically, 18 patients had squamous cell carcinomas, 16 had adenocarcinomas and 2 had small cell carcinomas. The median primary tumor diameter was 4.1 cm, with a maximum of 7.7 cm. In addition, a bulky mass was detected in 28 patients. In 13 patients, hydronephrosis was noted, with 8 of these having bilateral hydronephrosis. The number of distant metastases was 1 in most patients, but 3 or 4 in some patients. The metastatic lesion sites included the para-aortic node in 7 patients and the main organs in 8 patients. Table II shows the sites of distant metastases (including duplicating patients). In the abdominal cavity, para-aortic lymph node metastases were detected in 18 patients (50%), comprising the highest percentage. In the extraperitoneal region, supraclavian lymph node metastases were detected in 13 patients (36%). Among main organ metastases, liver metastases were detected in 7

Table I. Patient characteristics.

Age (year), median (range)	54 (28-77)
PS 0/1/2/3	5/18/11/2
No. of patients	36
Initial treatment	
Surgery	4
Radiotherapy	17
Chemotherapy	13
Best supportive care	2
Pathology	
Squamous cell carcinoma	18
Adenocarcinoma	16
Small cell carcinoma	2
Primary tumor size (cm), median (range)	4.1 (2.1-7.7)
Bulky mass >4 cm	
Negative	8
Positive	28
Hydronephrosis	
Negative	23
Unilateral	5
Bilateral	8
No. of distant metastases	
1	20
2	13
3	2
4	1
Site of distant metastases	
Para-aortic lymph node only	7
Distant lymph node only	7
Organ metastases only	1
Para-aortic lymph node + Distant lymph node	10
Para-aortic lymph node + Organ metastases	1

Table II. Distant metastases in patients.

Metastatic sites	n (%)
Intra-abdominal metastases	
Para-aortic lymph node	18 (50)
Liver	7 (19)
Spleen	2 (5.5)
Small intestine	1 (2.7)
Extra-abdominal metastases	
Lung	4 (11)
Bone	2 (5.5)
Supraclavicular lymph node	13 (36)
Mediastinal lymph node	2 (5.5)
Inguinal lymph node	2 (5.5)

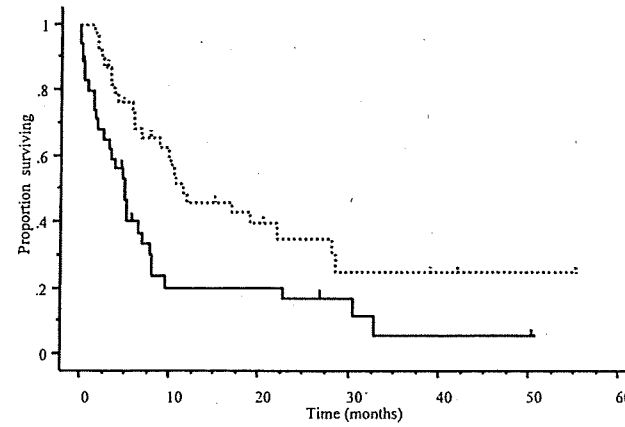

Figure 1. Kaplan-Meier analysis of progression-free survival (solid line) and overall survival (dotted line). Vertical bars indicate censored cases.

Table III. Characteristics of 21 patients with chemotherapy.

	n=21
Indication for therapy	
Initial case	13
Persistent/recurrence case	7
Postoperative case	1
Regimens	
Paclitaxel/carboplatin	9
Irinotecan/carboplatin	9
Weekly paclitaxel/carboplatin	2
Irinotecan/cisplatin	1

patients, comprising the highest percentage, followed by lung metastases in 4 patients. The median progression-free survival and overall survival were 3.8 months and 11.1 months, respectively (Fig. 1).

We examined the effects of chemotherapy on stage IVb cancer (Table III). Chemotherapy was administered to 21 patients, 13 of whom were undergoing initial treatment, 7 of whom had persistent/recurrence, and 1 of whom was undergoing postoperative therapy. The regimens consisted of paclitaxel/carboplatin in 9 patients, irinotecan/carboplatin in 9, weekly paclitaxel/carboplatin in 2, and cisplatin/irinotecan in 1. In 2 patients, including 1 undergoing postoperative adjuvant therapy, chemotherapy was discontinued due to adverse effects. For lesions that could be measured, the response rate was 61.9% (95% CI, 41.1-82.6) including 4 patients with CR and 9 patients with PR (Table IV).

We compared survival in the chemotherapy and non-chemotherapy groups. The median survivals of the chemotherapy and non-chemotherapy groups were 11.1 and 5.1 months, respectively, with a significant difference (p=0.0055) (Fig. 2).

We also compared survival between initial chemotherapy and initial other treatment groups. The median survivals in the initial chemotherapy and initial other treatment groups

Table IV. Response rate of chemotherapy (n=21).

Response (%)					
CR	PR	SD	PD	NE	RR
4	9	4	1	3	61.9%
					(95% CI, 41.1-82.6%)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; RR, response rate.

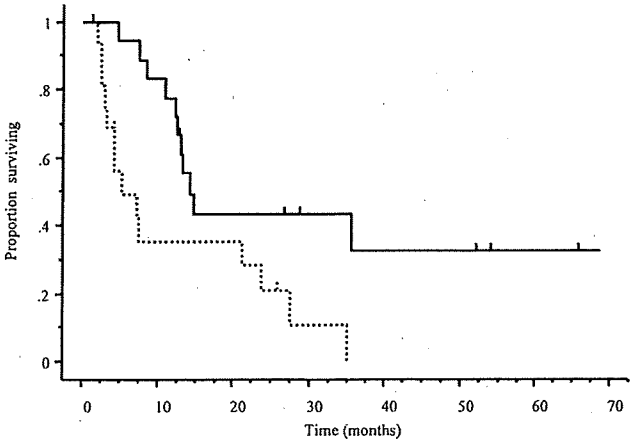

Figure 2. Kaplan-Meier analysis of overall survival according to with/without chemotherapy in stage IVb cervical carcinoma. Chemotherapy group (solid line) is significantly better prognosis (p=0.0055) than non-chemotherapy group (dotted line). Vertical bars indicate censored cases.

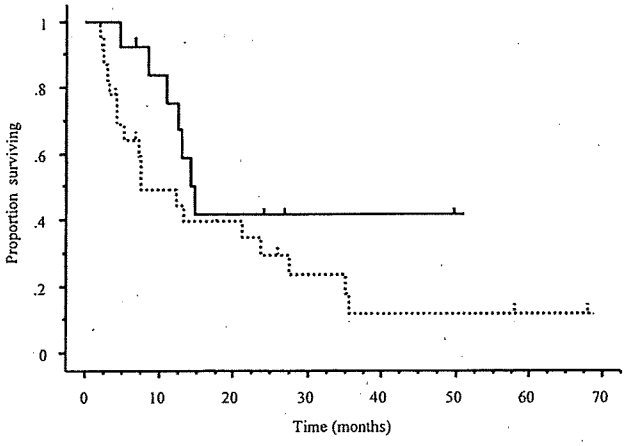

Figure 3. Kaplan-Meier analysis of overall survival according to with/without initial chemotherapy in stage IVb cervical carcinoma. There are no statistical differences (p=0.09) between initial chemotherapy group (solid line) and other initial treatment group (dotted line). Vertical bars indicate censored cases.

were 13.2 and 7.5 months, respectively, but it did not reach statistical significant (p=0.09) (Fig. 3). Two patients treated by chemotherapy alone as an initial treatment have survived

Table V. Prognostic factors of overall survival.

	Univariate	Multivariate		
Factor	P-value	P-value	HR	95% CI
Age ≥50	0.171	0.506	1.36	0.54-3.43
PS (0 and 1 vs. 2 and 3)	0.005	0.007	2.64	1.42-4.91
Pathology (SCC vs. non-SCC)	0.638	-	-	-
Organ metastases (0 vs. ≥1)	0.792	-	-	-
No. of distant metastases (1 vs. ≥2)	0.109	0.546	1.22	0.63-2.35
Bulky mass	0.478	-	-	-
Chemotherapy	0.011	0.016	6.03	1.97-18.37

disease-free for 51.8 and 68.6 months, respectively. One patient had stage IVb CC with para-aortic lymph node metastases while the other had stage IVb CC with subclavian lymph node metastases and mediastinal lymph node metastases. Both patients were administered paclitaxel/carboplatin for 6 cycles. After 6 cycles, the primary lesion and metastatic site exhibited complete response.

We analyzed chemotherapy, age, PS, histological type, main organ metastases, number of distant metastases, and bulky masses as prognostic factors. On univariate analysis, poor PS and non-chemotherapy groups were prognostic factors. On multivariate analysis, a poor PS (p=0.007; hazard ratio, 2.64; 95% CI, 1.42-4.91) and non-chemotherapy groups (p=0.016; hazard ratio, 6.03; 95% CI, 1.94-18.37) also affected overall survival (Table V).

Discussion

The prognosis of stage IVb cervical carcinoma is poor in patients with systemic metastases. No treatment has been established. In the NCI-PDQ, it is described that therapeutic strategies for this stage of cancer include palliative radiotherapy, chemotherapy as a regimen designed by a clinical study, and chemotherapy with cisplatin, which has previously been reported (34).

In stage IVb patients with para-aortic lymph node metastasis alone, surgery with postoperative radiotherapy and extended radiotherapy achieved a 5-year survival rate of 50% (30-33), and radical surgery may also be an option. However, since most metastases involve the main organs, it is difficult to control them by local treatment, and chemotherapy is indicated for most patients (4).

Various regimens of chemotherapy for this stage of cancer, including single-agent, have been investigated. In particular, cisplatin has most frequently been employed, and yields the highest response rate as a single-agent. It has therefore been

used as a key drug for more than 20 years (5,8,10-12). However, since the efficacy of cisplatin as a single-agent persists for only 6 months, combination regimens have been administered to improve in the prognosis to an extent exceeding the enhancement of its toxicity. In the 1990s, many phase II clinical studies investigated combination regimens with 2-4 agents including cisplatin. Cisplatin with ifosfamide (IFM) yielded the second highest response rate, and bleomycin (BLM), which has commonly been employed to treat other cancers due to its similar high response rate and low toxicity. The usefulness of IP (IFM + CDDP) (35) and BIP (BLM + IFM + CDDP) (36) regimens has also been examined. Some regimens have achieved a response rate of 60% or higher; however, these regimens for the non-advanced and locally advanced stages are quite toxic and shorten the survival of some patients. In addition, no comparative study has been conducted, and the evaluation of each regimen has been insufficient. In the latter half of the 1990s, combination regimens with new agents were designed, and the need for a standard therapy was emphasized.

Recently, carboplatin (37-39), topotecan (19,20) and paclitaxel (40-42) have also been reported to be tolerable and efficacious. Complete responses have also been observed with topotecan and paclitaxel. However, topotecan has greater toxicity than carboplatin or paclitaxel. Therefore, palliation with single-agent cisplatin, carboplatin, paclitaxel or topotecan is a reasonable approach in patients with recurrent disease. A phase II study evaluating the effectiveness of docetaxel in patients who have persistent or recurrent cervical cancer is ongoing (GOG-0127S).

Cisplatin-based combination chemotherapy regimens such as cisplatin/paclitaxel (21) and cisplatin/topotecan (22) have been extensively investigated in clinical studies. A randomized phase III study comparing paclitaxel and cisplatin versus cisplatin alone showed that the two-drug combination yielded a higher response rate (36 versus 19%) and improved progression-free survival (4.8 versus 2.8 months; $p<0.001$), although no improvement has been seen in median survival (21). Another randomized phase III GOG study investigated the combination of cisplatin and topotecan versus cisplatin alone for persistent/recurrent cervical cancer. In this study of 294 eligible patients, the topotecan combination regimen was superior to single-agent cisplatin with respect to overall response rate (27 versus 13%; $p=0.004$), progression-free survival (4.6 versus 2.9 months; $p=0.014$), and median survival (9.4 versus 6.5 months; $p=0.017$) (22). A phase II study assessed cisplatin and gemcitabine in patients with advanced, persistent/recurrent cervical cancer; 17 patients were evaluated (43). The response rate was 57% in patients who had not previously received radiotherapy, and there was 1 complete response of 14 months. Paclitaxel and carboplatin have recently been assessed for recurrent or persistent cancer of the cervix; 4 of 15 patients had a complete response and 5 showed a partial response for an overall response rate of 60% (39). The median survival of all 15 patients treated was 17 months (range, 4-39 months). The combination of vinorelbine and cisplatin has also been assessed in 42 patients with recurrent or metastatic cervical cancer; the overall response rate was 48% (44). The GOG is currently conducting a phase III trial (GOG204) to assess 4 cisplatin-doublet regimens in patients with advanced metastatic or recurrent cancer (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, versus cisiplatin/vinorelbine).

In our hospital, we conducted an in-house clinical study. For eligible patients, paclitaxel/carboplatin or irinitecan/carboplatin therapy was administered. Adverse effects were within the permissible ranges, and there were no treatment-related deaths, as reported in other studies. Response rate as an end-point was also similar to or exceeded that previously reported, suggesting the usefulness of these treatment options in chemotherapy for cervical carcinoma. In patients with poor PS, weekly paclitaxel/carboplatin therapy was safe. Several reports have indicated that the hematological toxicity of this therapy is lower than that of tri-weekly therapy, and that the therapeutic effects of these two regimens are similar (45,46). Weekly paclitaxel/carboplatin therapy may be useful for treating stage IVb cancer patients with poor PS.

In patient with this stage of cancer, nephropathy is frequent, making cisplatin administration difficult in many cases. Carboplatin can be administered to patients with nephropathy, without hydration. Considering the adverse effects, less toxic agents should be reviewed.

In this study, two patients treated by chemotherapy alone as an initial treatment have survived disease-free for 51.8 and 68.6 months, respectively. For patients with recurrence who desired sequential treatment, chemotherapy was administered when we considered them eligible. Considering that the prognosis was significantly better than that in the non-chemotherapy group, chemotherapeutic intervention may be useful in stage IVb patients who have undergone initial treatment and in those with persistent/recurrent metastases.

Eligible, consenting patients should be enrolled in clinical trials employing new drugs and/or strategies. Since there is as yet no evidence for the curative potential of chemotherapy in cervical cancer and no established survival benefit, and uncertainty exists as to how often response translates into symptom relief ('palliation'), non-protocol therapy should not be encouraged. Nevertheless, for a patient who is ineligible or unwilling to participate in a study but who wants treatment, there may still be an indication for chemotherapy giving 'psychological support' or hope. When such a patient insists on treatment and seeks untested remedies rather than a hospice if orthodox chemotherapy is not offered, single-agent cisplatin or carboplatin may be justified, with due attention being paid to contraindications and the toxic side effects. An interval response assessment and finite period of treatment are indicated. Objective benefit is possible, but not likely.

Prognostic factors for stage IVb cervical carcinoma include PS, age, histological type, main organ metastases, and distant metastases (23-29). In this study, univariate and multivariate analysis revealed that non-chemotherapy and poor PS influenced prognosis. In patients with poor PS, it is difficult to continue treatment, and chemotherapy may exceed cancer control due to systemic disease. However, we can not conclude the efficacy of chemotherapeutic intervention, as this study was a retrospective study and involved only a small number of patients. Previously, surgery and radiotherapy have been selected for this stage of cancer. The results of chemotherapy for initial treatment were similar to those for conventional treatment, suggesting the efficacy of chemotherapy as initial

treatment. However, a randomized comparative study should be conducted to demonstrate its efficacy.

In conclusion, the prognosis of stage IVb cervical carcinoma remains poor. Chemotherapy may improve the survival of patients with stage IVb CC.

Acknowledgments

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Original Article

The prevalence of intrinsic subtypes and prognosis in breast cancer patients of different races

Junichi Kurebayashi[a,b,*], Takuya Moriya[b,c], Takanori Ishida[d], Hisashi Hirakawa[e], Masafumi Kurosumi[b,f], Futoshi Akiyama[b,g], Takayuki Kinoshita[b,h], Hiroyuki Takei[b,i], Kaoru Takahashi[b,j], Masahiko Ikeda[a], Kazutaka Nakashima[a,b]

[a]*Department of Breast and Thyroid Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan*
[b]*The Special International Project Team of the Japanese Breast Cancer Society*
[c]*Department of Pathology, Tohoku University Hospital, Aoba-ku, Sendai, Japan*
[d]*Department of Surgical Oncology, Tohoku University Hospital, Aoba-ku, Sendai, Japan*
[e]*Department of Surgery, Tohoku Kosai Hospital, Aoba-ku, Sendai, Japan*
[f]*Department of Pathology, Saitama Cancer Center, Kita-Adachi, Saitama, Japan*
[g]*Department of Breast Pathology, Cancer Institute of Japanese Foundation for Cancer Research, Tokyo, Japan*
[h]*Division of Surgical Oncology, National Cancer Center Hospital, Tokyo, Japan*
[i]*Division of Breast Surgery, Saitama Cancer Center, Kita-Adachi, Saitama, Japan*
[j]*Division of Breast Surgery, Shizuoka Cancer Center, Sunto-gun, Shizuoka, Japan*

Abstract

A recent report indicated that a high prevalence of basal-like breast tumors (estrogen receptor [ER]-negative, progesterone receptor [PR]-negative, human epidermal growth factor receptor [HER] 2-negative, and cytokeratin 5/6-positive and/or HER1-positive) could contribute to a poor prognosis in African American women with breast cancer. It has been reported that Japanese women with breast cancer have a significantly better survival rate than other races in the USA. These findings suggest that breast cancers in Japanese women have favorable biological characteristics. To clarify this hypothesis, we conducted a cohort study to investigate the prevalence of intrinsic subtypes and prognosis for each subtype in 793 Japanese patients. This study revealed a very low prevalence (only 8%) of basal-like breast tumors with aggressive biological characteristics in Japanese patients. Survival analysis showed a significantly poorer prognosis in patients with basal-like tumors than in those with luminal A tumors (ER- and/or PR-positive, and HER2-negative) with favorable biological characteristics. These findings support the hypothesis that breast cancers in Japanese women have more favorable biological characteristics and a better prognosis than those in other races. In conclusion, the prevalence of basal-like breast tumors could influence the prognosis of breast cancer patients of different races. The prevalence of intrinsic subtypes should be taken into account when analyzing survival data in a multi-racial/international clinical study.

Keywords: Breast cancer; Intrinsic subtype; Triple-negative tumor; Prevalence; Japanese; Prognosis

Introduction

Although breast cancer survival has improved over the past 20 years in some developed countries,[1] significant differences in breast cancer stage, treatments, and mortality rates still exist in the world with regard to race and ethnicity.[2] The causes of survival difference are likely to be multifactorial including socio-economical factors, differences in access to insurance, screening and treatments, and biological differences among breast cancers themselves. These biological differences may reflect genetic influences and differences in lifestyle, nutrition or environmental exposure.

A number of studies have investigated the causative factors leading to racial disparity in breast cancer survival

*Corresponding author. Department of Breast and Thyroid Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan. Tel.: +81 86 462 1111; fax: +81 86 462 1199.
E-mail address: kure@med.kawasaki-m.ac.jp (J. Kurebayashi).

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between African American (AA) and white American patients in the USA. Possible explanations include aggressive phenotypes of breast tumors,[3–5] such as high-grade and estrogen receptor (ER)-negative (ER−), patient characteristics,[6,7] such as obesity and a higher rate of co-morbidity, inadequate mammmographic screening,[8,9] delay of diagnosis leading to advanced stage,[10,11] and inadequate treatment,[12–14] such as not meeting treatment guidelines in AA women; however, these factors are unable to totally elucidate the disparity. Interestingly, a recent report indicated that a higher prevalence of basal-like breast tumors (ER−, progesterone receptor negative [PR−], human epidermal growth factor receptor 2-negative [HER2−], cytokeratin [CK] 5/6-positive, and/or HER1-positive [HER1+]), which have aggressive biological phenotypes and a poor outcome, and a lower prevalence of luminal A tumors (ER+ and/or PR+, and HER2−), which have an estrogen-responsive phenotype and a favorable outcome, could contribute to a poorer prognosis in young AA women with breast cancer.[15]

In contrast to AA patients, according to the Hawaii Tumor Registry of the Surveillance, Epidemiology, and End Results Program in the USA, Japanese patients with breast cancer have a significantly better survival rate than patients of other races after controlling for age, stage, and ER/PR status. There are no differences, however, in the survival rates of Chinese, Filipino, and Caucasian women.[16] These findings suggest that breast cancers in Japanese women have favorable biological characteristics, such as a lower prevalence of basal-like breast tumors. To clarify this hypothesis, we conducted a retrospective cohort study to investigate the prevalence of intrinsic subtypes of breast tumors and prognosis for each subtype in Japanese breast cancer patients.

Patients and methods

Study patients

The goal of the present study was to estimate the prevalence of breast cancer subtypes in Japanese breast cancer patients, and to examine correlations between clinico-pathologic variables and survival. Clinico-pathologic data of a cohort of consecutive Japanese patients with invasive breast cancer treated between January 2000 and December 2003 were collected from three different institutes, Kawasaki Medical School Hospital, Tohoku University Hospital, and Tohoku Kousai Hospital in Japan. The study procedures were approved by the institutional review board of each hospital.

Based on the histologic records, tumors were classified into two categories: invasive ductal carcinomas not otherwise specified (NOS) and others. The American Joint Committee on Cancer (AJCC, 5th edition) stage and lymph node status were collected from the medical records. Histologic grading was according to the modified Bloom and Richardson method by Elston and Ellis (Nottingham's grading system).[17] Lymph vessel invasion (LVI) was assessed using hematoxylin–eosin-stained glass slides. Vascular channels lined by thin endothelial cells, especially close to the small arteries and veins, were considered as lymph vessels, and tumor emboli were floating in the lumen in LVI-positive cases. Most LVI were seen at the periphery of the invasive tumors.[18] Blood vessel invasion (BVI) was evaluated using elastica Masson stain or immunostaining for CD34. Tumor cell nests surrounded by elastic fibers and the wall of smooth muscle, next to the small arteries (but not mammary ducts with multilayered elastic fibers) were considered as positive.[18]

Immunohistochemical (IHC) subtypes

ER and PR status were determined by IHC performed at each institute. The cutoffs for receptor positivity were 10%. The HER2 status was also determined by IHC at each institute. According to the criteria of the HecepTest, scores 0 and 1 were considered negative, and scores 2 and 3 were considered positive.[19] Triple-negative (ER−, PR−, and HER2−) breast cancer samples were examined by IHC for CK 5/6 and HER1. CK 5/6 and HER1 were considered positive when more than 10% of the tumor cells were labeled. First antibodies and IHC procedures are presented in Table 1.

According to Carey et al.,[15] IHC intrinsic subtypes were defined as follows: luminal A (ER+ and/or PR+, HER2−), luminal B (ER+ and/or PR+, HER2+), basal-like (ER−, PR−, HER2−, CK 5/6-positive, and/or HER1+), HER2+/ER−, and unclassified (negative for all five markers).

Statistical analysis

Differences between breast cancer subtypes with regard to clinico-pathologic characteristics were examined using analysis of variance, χ^2 tests or Fisher's exact test. Survival curves were generated using the Kaplan–Meier method, and the log-rank test was used to compare mean survival across IHC subtypes. StatView statistical software was used to manage and analyze data. Statistical differences were considered significant at $P \leqslant 0.05$.

Results

IHC subtypes and characteristics of patients

Clinico-pathologic data on 793 Japanese patients with invasive breast cancer were collected from three hospitals in Japan. The characteristics of the patients with IHC data, overall and according to IHC subtypes, are presented in Table 2. IHC subtypes differed significantly by age ($P = 0.025$), AJCC stage ($P < 0.001$), histologic grade ($P < 0.001$), LVI ($P = 0.018$), and BVI ($P = 0.026$). Patients with the basal-like subtype were younger than patients with the HER2+/ER− subtype. Patients with basal-like tumors were more likely to be in the more advanced stage, and to have tumors with a higher histologic grade or BVI than patients with luminal A tumors.

Table 1
Source, dilution, pretreatment and cutoff values of antibodies used

Antibody, clone	Dilution	Source	Pretreatment	Cutoff values
ER [1D5]	1:400	IMMUNOTECH	Autoclaved	⩾10% (positive)
PR [636]	1:2000	DAKO	Autoclaved	⩾10% (positive)
HER2 [HercepTest]	NA*	DAKO	None	NA
HER1 [2-18C9]	NA	DAKO	Proteinase K	⩾10% (positive)
CK 5/6 [D5/16134]	1:100	DAKO	Autoclaved	⩾10% (positive)

*Not assessable.

Table 2
Prevalence of intrinsic subtypes and clinico-pathological characteristics in Japanese breast cancer patients

	All cases	Luminal A	Luminal B	HER2+/ER−	Basal-like	Unclassified	*P* value*
No. of cases	793	502 (63)†	155 (20)	55 (7)	67 (8)	14 (2)	
Age, median (range), years-old	54 (19–88)	53 (27–88)	53 (19–85)	60 (31–84)	54 (30–79)	50 (36–66)	0.025
AJCC stage							<0.001
I	289	213	48	4	18	6	
II	360	208	70	39	38	5	
III	68	36	17	4	8	3	
IV	40	19	15	4	2	0	
Missing	36	26	5	4	1	0	
Histology							0.142
Invasive ductal carcinoma NOS	721	447	149	53	60	12	
Specific types	70	54	5	2	7	2	
Missing	2	1	1	0	0	0	
Histologic grade							<0.001
I	156	131	23	0	1	1	
II	320	235	56	15	11	3	
III	197	61	48	33	49	6	
Missing	120	75	28	7	6	4	
LVI							0.018
Positive	345	212	69	32	27	5	
Negative	373	249	62	20	36	6	
Missing	75	41	24	3	4	3	
BVI							0.026
Positive	126	82	18	10	14	2	
Negative	570	267	105	40	49	9	
Missing	97	53	32	5	4	3	
Nodal status							0.572
Positive	303	184	62	25	27	5	
Negative	437	286	78	25	29	9	
Not applicable or missing	53	32	15	5	1	0	
Outcome							
Follow-up, median (range), months	46.5 (1–84)						
5-year DFS	85.5%	90.3%	82.9%	62.1%	77.1%	81.8%	<0.001‡
5-year OS	92.8%	96.9%	86.6%	86.9%	86.2%	83.3%	<0.001‡

*Comparing five subtypes using χ^2 test or Fisher's exact test.
†In %.
‡Log-rank test.

Survival by IHC subtypes

Survival data on 786 of 793 patients with invasive breast cancer were available from three hospitals. The duration of follow-up was 1–84 months (median, 46.5). During this period, recurrence was observed in 91 patients, and 48 patients died of any causes.

Breast cancer subtypes significantly differed in 5-year disease-free survival (DFS, $P<0.001$): luminal A (90.3%), luminal B (82.9%), HER2+/ER− (62.1%), basal-like

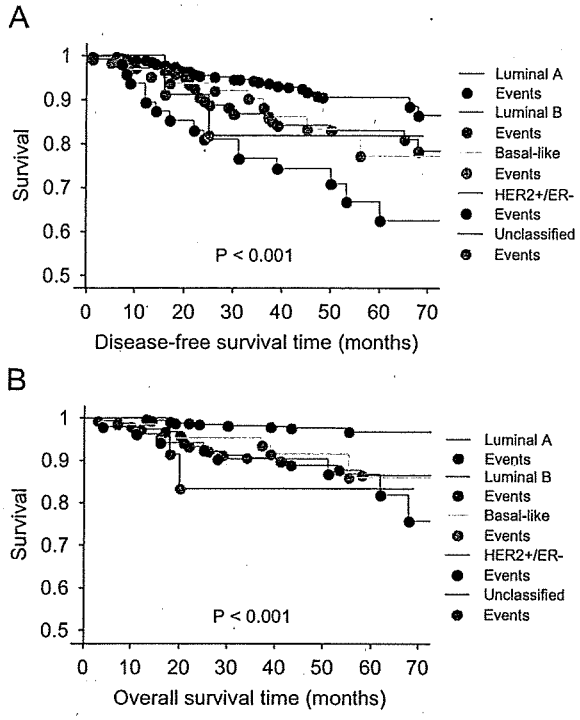

Fig. 1. DFS (A) and OS (B) curves in breast cancer patient groups divided by IHC intrinsic subtypes.

subtype (77.1%), and unclassified (81.8%). They also differed in 5-year overall survival (OS, $P<0.001$): luminal A (96.9%), luminal B (86.6%), HER2+/ER− (86.9%), basal-like subtype (86.2%), and unclassified (83.3%). Kaplan–Meier survival curves are presented in Fig. 1. Both DFS and OS were significantly worse among basal-like and HER2+/ER− breast cancer patients compared with luminal A patients.

Differences in DFS and OS by IHC subtypes were seen among lymph node-positive patients ($P = 0.006$ for DFS and $P<0.001$ for OS) but not lymph node-negative patients; however, the number of patients after stratifying by lymph node status was limited and these data should be interpreted with caution. Five-year DFS within lymph node-positive patients by subtype was as follows: luminal A (79.3%), luminal B (71.2%), HER2+/ER− (35.2%), basal-like subtype (68.1%), and unclassified (50.0%). Five-year OS within lymph node-positive patients was as follows: luminal A (96.3%), luminal B (75.6%), HER2+/ER− (84.1%), basal-like subtype (83.9%), and unclassified (60.0%).

Discussion

Carey et al. have recently reported for the first time the population-based prevalence of intrinsic subtypes of breast tumors. They refined an IHC-based assay to identify breast tumor intrinsic subtypes instead of gene expression profiling.[15] This IHC-based assay has been verified against gene expression profiles to estimate the prevalence of intrinsic subtypes.[15,20] Additionally, large-scale subtyping using gene expression profiling from formalin-fixed, paraffin-embedded samples is not currently feasible; therefore, we conducted this cohort study to investigate the prevalence of intrinsic subtypes using the IHC-based assay in Japanese breast cancer patients.

According to Carey et al.,[15] the prevalence of basal-like and luminal A tumors in the Carolina Breast Cancer Study was 27% and 47% in AA patients and 16% and 54% in non-AA patients, respectively. Since breast cancer-specific survival was significantly worse in patients with basal-like tumors than with luminal A tumors, the higher prevalence of a basal-like subtype could contribute to a worse prognosis in AA patients. Moreover, the prevalence of basal-like and luminal A tumors was 39% and 36% in premenopausal AA patients, respectively. In contrast, the prevalence of basal-like and luminal A tumors was 8% and 63% in Japanese breast cancer patients, respectively, in the present study. The prevalence of basal-like tumors was 2–3 times lower in Japanese patients than in non-AA patients or AA patients. In addition, the prevalence of luminal A tumors was 9–16% higher in Japanese patients than in non-AA patients or AA patients. Breast cancer patients with basal-like tumors had a poorer prognosis in terms of DFS and OS than those with luminal A tumors in the present study (Fig. 1) as previously indicated in the report by Carey et al.[15] These findings have suggested that the lower prevalence of basal-like tumors and higher prevalence of luminal A tumors in Japanese patients could contribute to their better prognosis.

A limited number of studies have investigated the prevalence of intrinsic subtypes by the IHC-based assay in different races. On the other hand, the prevalence of triple-negative breast tumors has recently become available. Triple-negative tumors include both basal-like and unclassified tumors. The prevalence of basal-like tumors was reported to be approximately 70% in triple-negative tumors[15]; it was 78% in the present study. The prevalence of triple-negative tumors was 22% in the Carolina Breast Cancer Study,[15] 16% in a large series of patients in the UK,[21] 26% in conservatively managed patients in the USA,[22] and 31% in consecutive patients in Korea.[23] In the present study, the prevalence of triple-negative tumors was only 10%, 1.6–3 times lower in Japanese patients than in patients of other races. These findings also support the lower prevalence of basal-like tumors in Japanese patients.

Differences in genetic influences or lifestyle may explain the prevalence of intrinsic subtypes among different races. Differences in the distribution of breast cancer risk factors, such as breast cancer family history, age at menarch, age at first birth, body mass index, and hormone replacement therapy, have been extensively investigated, and these differences may explain differences in breast caner incidence rates among different races.[5] However, the investigation of causative factors leading to differences in the prevalence of intrinsic subtypes in different races remains

to be investigated. Because of a close correlation between the prevalence of intrinsic subtypes and the prognosis of breast cancer patients indicated by us and others,[15,20] nutritional or environmental factors influencing the prevalence may provide hints for developing new intervention strategies to reduce breast cancer mortality rates. It has been indicated that the intake of green tea or soy beans relates to a reduction in breast cancer incidence rates.[24,25] Furthermore, the consumption of green tea was suggested to correlate with not only a reduction in breast cancer incidence but also improved outcome of breast cancer patients in Japanese women.[26] In addition, it is suggested that breast cancer patients with a high intake of green tea tend to have less aggressive and hormone-responsive breast tumors.[27] Interestingly, recent experimental studies have revealed that green tea extracts such as (−)-epigallocatechin gallate have significant anti-tumor activity in breast cancer cells with basal-like phenotypes.[28–30] These findings suggest that green tea intake may modify the biological characteristics of breast tumors and the prevalence of intrinsic subtypes. Further epidemiologic and experimental studies are warranted to investigate the role of green tea intake in breast cancer development and progression.

In conclusion, the present study suggests for the first time that a lower prevalence of basal-like breast tumors and a higher prevalence of luminal A breast tumors could contribute to a favorable prognosis of Japanese breast cancer patients. Taken together with the worse prognosis of AA patients having a higher prevalence of basal-like tumors and a lower prevalence of luminal A tumors, it could be concluded that the prevalence of intrinsic subtypes differs among different races and such a difference may explain differences in the prognosis of breast cancer patients of different races. From the clinical point of view, the prevalence of intrinsic subtypes should be taken into account when analyzing survival data in a multi-racial/international clinical study. In addition, causative factors influencing the prevalence of intrinsic subtypes should be explored to develop intervention strategies to reduce breast cancer incidence and the mortality rate.

Conflict of Interest Statement

None declared.

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Clinical Trial Note

Accelerated Fractionation versus Conventional Fractionation Radiation Therapy for Glottic Cancer of T1-2N0M0 Phase III Study: Japan Clinical Oncology Group Study (JCOG 0701)

Kenichi Nakamura[1], Takeshi Kodaira[2], Naoto Shikama[3], Yoshikazu Kagami[4], Satoshi Ishikura[1], Taro Shibata[1] and Masahiro Hiraoka[5]

[1]Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, [2]Department of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya, [3]Department of Radiology, Shinshu University School of Medicine, Nagano, [4]Radiation Oncology Division, National Cancer Center Hospital, Tokyo and [5]Department of Radiation Oncology and Image-applied Therapy, Kyoto University Hospital, Kyoto, Japan

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A randomized Phase III study was started in Japan to demonstrate the non-inferiority of survival of accelerated fractionation radiation therapy (2.4 Gy/fr) with conventional fractionation radiation therapy (2 Gy/fr) in patients with T1-2N0M0 glottic cancer. This study began in September 2007, and a total of 360 patients will be accrued from 22 institutions within 4 years. The primary endpoint is 3-year progression-free survival (PFS). The secondary endpoints are overall survival, local progression-free survival, disease-free survival, survival with preserved voice function, complete response rate, proportion of treatment completion and adverse events.

Key words: laryngeal neoplasms – radiotherapy – dose fractionation – clinical trials – phase III

INTRODUCTION

Accelerated fractionation radiation therapy has considerable benefits in terms of treatment duration and cost compared with conventional fractionation methods. In addition, some reports suggest that increased single radiation dose and shortened treatment time may improve local control (1–7). However, no multi-institutional randomized study has been conducted to show that accelerated fractionation is equivalent to conventional fractionation in terms of efficacy and safety for early glottic cancer. Various types of fractionation methods are performed in clinical practice, and according to the guidelines of the Head and Neck Cancer Disease Site Group in Canada, an optimal fractionation protocol has not yet been established (8). We therefore designed a study, which investigates whether accelerated fractionation radiotherapy is suitable for T1-2N0M0 glottic cancer in terms of survival, feasibility, voice function and safety.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in August 2007 and the study was activated in September 2007. This trial was registered at the UMIN Clinical Trials Registry as UMIN000000819 [http://www.umin.ac.jp/ctr/index.htm].

For reprints and all correspondence: Takeshi Kodaira, Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, 464-8681, Japan. E-mail: 109103@aichi-cc.jp

PROTOCOL DIGEST OF THE JCOG 0701

Purpose

The aim of this study is to demonstrate the non-inferiority of the efficacy of accelerated fractionation radiation therapy (2.4 Gy/fr) with conventional fractionation radiation therapy (2 Gy/fr) in patients with T1-2N0M0 (UICC/TNM, 6th edition) glottic squamous cell carcinoma.

Study Setting

A multi-institutional randomized Phase III study.

Resources

Grants-in-Aid for Cancer Research (17-17, 16-12, 17S-5) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint is the 3-year progression-free survival (PFS) proportion in all eligible patients. PFS is defined as days from randomization to first evidence of local progression, distant metastasis or death from any cause. In patients alive without events, PFS will be censored at the last visit. The secondary endpoints are overall survival, local progression-free survival, disease-free survival, survival with preserved voice function, complete response rate, proportion of treatment completion and adverse events.

Overall survival is defined as days from randomization to death from any cause. Local progression-free survival consists of time free from local disease progression or death from any cause, while disease-free survival is defined as duration free of local progression, distant metastasis, secondary cancer or death from any cause. Survival with preserved voice function is defined as days from randomization to first evidence of death from any cause or appearance of voice changes of Grade 3 or more as diagnosed by the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). The proportion of treatment completion denotes the percentage of patients whose treatment is completed within the recommended length of time: 51 days for T1 and 53 days for T2 in the conventional radiation arm, and 39 days for T1 and 43 days for T2 in the accelerated radiation arm.

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, the patient must fulfill each of the following criteria: (i) primary tumor site lies within the vocal cords; (ii) the tumor consists of histologically proven squamous cell carcinoma; (iii) the extent of the primary tumor is evaluated as T1 or T2 without impaired cord mobility; (iv) the tumor is clinically staged as N0/M0; (v) radiation therapy can be completed within the recommended duration without interruption due to national holidays; (vi) age between 20 and 80 years; (vii) ECOG performance status of 0 or 1; (viii) no prior surgery or radiation therapy of the larynx; (ix) no prior chemotherapy for any malignancies within 5 years; (x) sufficient organ function; (xi) completed written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) active bacterial or fungous infection; (ii) simultaneous or metachronous (within 5 years) double cancers; (iii) women during pregnancy or breast-feeding; (iv) psychosis; (v) treatment with systemic steroids; (vi) history of collagen disease except for rheumatism; (vii) insulin-dependent or poorly controlled diabetes mellitus; (viii) poorly controlled hypertension; (ix) history of severe heart disease, heart failure; (x) myocardial infarction or angina pectoris within the past 6 months.

Randomization

After the confirmation of the inclusion and exclusion criteria by telephone or fax to the JCOG Data Center, the patients are randomized to either conventional radiation arm or accelerated radiation arm, by the minimization method of balancing the arms according to T factor (T1/T2 by UICC/TNM, 6th edition) and institution.

Treatment Method

In conventional radiation arm, conventional fractionation radiotherapy with 2 Gy/fr (1 fr/day and 5 fr/week) is performed 33 times for a total dose of 66 Gy in patients with T1 disease, and 35 times for a total dose of 70 Gy in patients with T2 disease. Irradiation twice daily is permitted, but the maximum number of irradiation sessions per week is limited to five. It is recommended that treatment using the conventional fractionation method is completed within 51 days for T1 disease and 53 days for T2 disease.

In accelerated radiation arm, accelerated fractionation radiotherapy with 2.4 Gy (1 fr/day and 5 fr/week) is delivered 25 times for a total dose of 60 Gy in patients with T1 disease, and 27 times for a total dose of 64.8 Gy in patients with T2 disease. Twice-daily irradiation is prohibited, as is irradiation six or more times per week. Recommended duration of accelerated fractionation radiotherapy is 39 days for T1 disease and 43 days for T2 disease.

In both study arms, the gross tumor volume (GTV) is defined as the GTV of the primary tumor. The clinical target volume (CTV) in T1 disease is the entirety of the vocal cords, while the CTV in T2 disease includes a 1-cm margin surrounding the tumor in addition to the vocal cords. The planning target volume (PTV) is defined as the CTV plus a margin of 0.5-1 cm in the craniocaudal direction and 0.5 cm in the posterioanterior direction.

Follow-up

All enrolled patients are followed-up at least every 6 weeks for the first 6 months and then every 3 months for a duration of 3 years. Laryngeal fiberscope and cervical lymph node exploration by manipulation are carried out at each visit.

Study Design and Statistical Method

This trial is designed to demonstrate that accelerated fractionation radiation therapy is not inferior to the conventional fractionation method in terms of 3-year PFS. If the non-inferiority of accelerated radiation arm is verified, the accelerated fractionation method will be the preferred treatment.

The planned sample size is 360 patients, with 180 cases per arm. We anticipate 3 years of follow-up after 4 years of accrual, ensuring at least 80% power with one-sided alpha of 5% and a non-inferiority margin of 5% for the primary end-point. This assumes an expected 3-year PFS of 80% in patients treated with the conventional fractionation method, and 85% in those treated with the accelerated fractionation method.

Interim Analysis and Monitoring

We plan on conducting two interim analyses, considering multiplicity according to the method recommended by the Southwest Oncology Group (9). The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and stop the trial early if necessary. In-house monitoring will be performed every 6 months by the Data Center to evaluate and improve study progress and quality.

Participating Institutions (From North To South)

Sapporo Medical University, Tohoku University, Saitama Cancer Center, National Cancer Center East, National Cancer Center, Tokyo Metropolitan Komagome Hospital, Tokyo Women's Medical University, Tokyo Medical Center, Keio University, Cancer Institute Hospital, University of Tokyo, Kitasato University, Niigata Cancer Center, Yamanashi University, Shinshu University, Aichi Cancer Center, Kyoto University, Osaka University, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, Hiroshima University, Kyushu University.

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Conflict of interest statement

None declared.

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これからの乳癌診療

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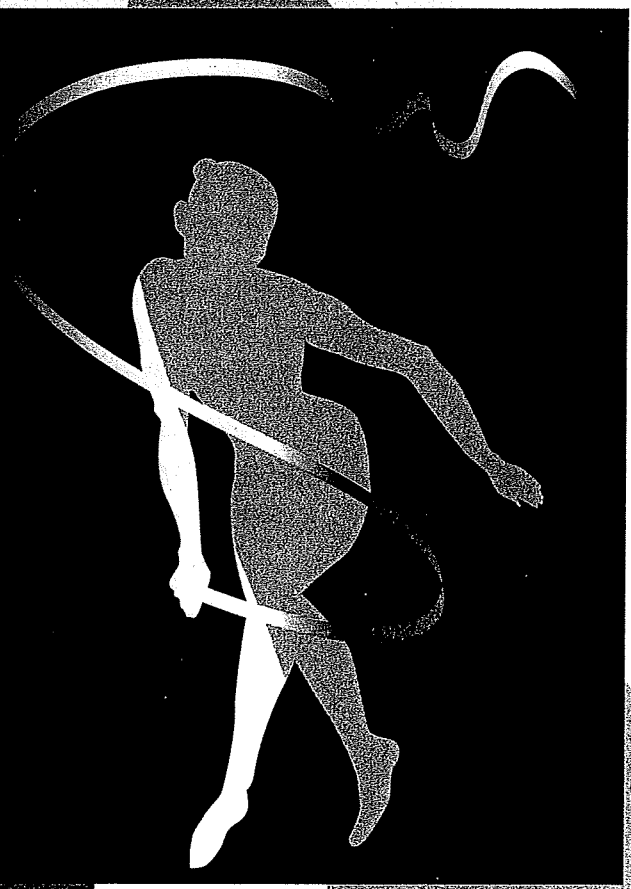

1.検診・診断

2.外科療法

3.薬物療法

4.放射線療法

5.疫学

6.トピックス

7.コメディカルに必要な最新の知識

金原出版

第4章

放射線療法

鹿間　直人・福田　護

言うまでもなく乳癌においては全身療法の役割は大きく，新規抗癌剤やホルモン療法，分子標的治療薬などが話題を集めている。固形癌において全身に広がった微小転移を制御できる有効な全身療法が行われた場合には，適切な局所療法を加えることで生存率の向上が期待できることが報告されており，有効な全身療法が登場している乳癌診療において局所療法としての放射線治療の役割はさらに重要となっている。

現在，患者の利便性を考慮し短期間で術後照射を終了させる乳房部分照射や全乳房短期照射は欧米を中心に研究が進んでおり，今後わが国の日常臨床でも普及するものと思われるが，解決しなければならない諸問題が内在している。今回は，このような治療法を日常臨床に導入するにあたり，注意しておかなければならないピットホールを中心に，お二人の先生方にご執筆をお願いした。

「乳癌診療ガイドライン」が発行され，現在改訂の時期にある。文献の抽出の際にはランダム化比較試験や大規模研究が重要視されるため海外からの論文が主に選択されており，今後わが国からの信頼性の高いエビデンスを発信する必要性が再確認された。乳房切除後の術後照射は二つの信頼性の高いランダム化比較試験で生存率の向上が証明され，わが国のガイドラインでも行うことが推奨されている。しかし，わが国の外科の先生方にはその必要性が十分に受け入れられておらず，術後照射の施行頻度は低い。人種差などが原因となり海外のエビデンスがわが国に当てはまらないためなのか，またエビデンスを臨床の現場に外挿する過程で何らかの問題があるのか，わが国発のエビデンスを持たない我々には解決し難い。しかし，このクリニカル・エビデンスギャップ(臨床とエビデンスの乖離)をいかに埋めていくかは臨床的に重要であり，田村先生には外科の立場からご自身の施設の成績も含めてご検討いただいた。

次々に新しい情報が発信される中，我々がその情報をどのように解釈し臨床の現場に取り入れていくかは重要な作業である。また，いまだ解決に至っていない事項に関しては，新たな研究課題であることは間違いない。

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PHYSICS CONTRIBUTION

IN VIVO DOSIMETRY OF HIGH-DOSE-RATE INTERSTITIAL BRACHYTHERAPY IN THE PELVIC REGION: USE OF A RADIOPHOTOLUMINESCENCE GLASS DOSIMETER FOR MEASUREMENT OF 1004 POINTS IN 66 PATIENTS WITH PELVIC MALIGNANCY

TAKAYUKI NOSE, M.D.,*† MASAHIKO KOIZUMI, M.D.,‡ KEN YOSHIDA, M.D.,§ KINJI NISHIYAMA, M.D.,‡ JUNICHI SASAKI,‡ TAKESHI OHNISHI,‡ TAKUYO KOZUKA, M.D.,* KOTARO GOMI, M.D.,* MASAHIKO OGUCHI, M.D.,* IORI SUMIDA, PH.D.,*† YUTAKA TAKAHASHI, PH.D.,† AKIRA ITO, PH.D.,† AND TAKASHI YAMASHITA, M.D.*†

*Department of Radiation Oncology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; †Department of Physics, The Cancer Institute of the Japanese Foundation for Cancer Research, Tokyo, Japan; ‡Department of Radiation Oncology, Osaka Medical Center, Osaka, Japan; and §Department of Radiology, Osaka National Hospital, Osaka, Japan

Purpose: To perform the largest *in vivo* dosimetry study for interstitial brachytherapy yet to be undertaken using a new radiophotoluminescence glass dosimeter (RPLGD) in patients with pelvic malignancy and to study the limits of contemporary planning software based on the results.

Patients and Methods: Sixty-six patients with pelvic malignancy were treated with high-dose-rate interstitial brachytherapy, including prostate ($n = 26$), gynecological ($n = 35$), and miscellaneous ($n = 5$). Doses for a total of 1004 points were measured by RPLGDs and calculated with planning software in the following locations: rectum ($n = 549$), urethra ($n = 415$), vagina ($n = 25$), and perineum ($n = 15$). Compatibility (measured dose/calculated dose) was analyzed according to dosimeter location.

Results: The compatibility for all dosimeters was 0.98 ± 0.23, stratified by location: rectum, 0.99 ± 0.20; urethra, 0.96 ± 0.26; vagina, 0.91 ± 0.08; and perineum, 1.25 ± 0.32.

Conclusions: Deviations between measured and calculated doses for the rectum and urethra were greater than 20%, which is attributable to the independent movements of these organs and the applicators. Missing corrections for inhomogeneity are responsible for the 9% negative shift near the vaginal cylinder (specific gravity = 1.24), whereas neglect of transit dose contributes to the 25% positive shift in the perineal dose. Dose deviation of >20% for nontarget organs should be taken into account in the planning process. Further development of planning software and a real-time dosimetry system are necessary to use the current findings and to achieve adaptive dose delivery. © 2008 Elsevier Inc.

Radiotherapy, *In vivo* dosimetry, Radiophotoluminescence glass dosimeter, Brachytherapy, High dose rate.

INTRODUCTION

Contemporary planning software for high-dose-rate (HDR) brachytherapy enables radiation oncology teams to determine conformal dose distribution to the target while avoiding excessive doses to critical organs (1–4); however, reproducibility of planned doses in interstitial brachytherapy has not been well recognized. Few studies have investigated *in vivo* dosimetry for interstitial brachytherapy; previous studies have dealt with small numbers of patients (≤10 patients, to the best of our knowledge) and have been limited to the use of thermoluminescence dosimeters (TLD), the use of which involves complex handling processes (5–9).

A radiophotoluminescence glass dosimeter (RPLGD) was developed in the 1950s and has subsequently been used for radiotherapeutic dosimetry at a small number of centers (10–14). Irradiation of silver-activated phosphate glass converts silver ions to stable luminescent centers; when exposed to ultraviolet light, the luminescent centers produce fluorescence in proportion to the absorbed radiation dose. RPLGDs possess ideal properties for *in vivo* dosimetry, including small

Reprint requests to: Takayuki Nose, M.D., Department of Radiation Oncology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, 3-10-6 Ariake, Koto-Ku, Tokyo 135-8550, Japan. Tel: (+81) 3-3520-0111; Fax: (+81) 3 3570 0343; E-mail: takayuki.nose@jfcr.or.jp

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size, ruggedness, nontoxicity, photon-energy independence over the energy range >0.2–0.3 MeV, high sensitivity, good reproducibility, and repeat readability until annealing of the detectors. Advances in technology (10–15) have helped to overcome initial shortcomings in the method, such as energy dependence in the low-energy range of <0.1 MeV, susceptibility to spurious readings with surface contamination, and the necessity for complex handling and cleaning processes. Newly developed RPLGDs (Dose Ace, Chiyoda Technol, Tokyo, Japan) were used in the current study (10–12). In our previous study, using RPLGD, we performed the largest *in vivo* dosimetry study examined at that time by measuring 83 points in 61 head and neck cancer patients (12). In the current study, we investigate the reproducibility of pelvic interstitial brachytherapy by measuring 1004 points in 66 pelvic malignancy patients. On the basis of the results, we investigated the limits of available planning software and a potential solution for precise dose delivery.

PATIENTS AND METHODS

Patients

Sixty-six patients with pelvic malignancy underwent HDR interstitial brachytherapy (HDRIB) with RPLGD at Osaka Medical Center (OMC) between 2000 and 2003. Patient characteristics are presented in Table 1. The median follow-up period was 30 months (range, 1–58 months). Forty-three patients displayed nonrecurrent disease, and 23 patients displayed recurrent disease following surgery ($n = 11$), radiation ($n = 4$), or both ($n = 8$). All patients were informed of the study purposes and possible consequences. Written informed consent was obtained before participation.

Radiophotoluminescence glass dosimeter

The RPLGD (Dose Ace) is more robust than TLDs and is composed of uniform glass with an effective atomic number of 12.039; it contains 11.00% Na, 31.55% P, 51.16% O, 6.12% Al, and 0.17% Ag by weight (10). The element is 1.5 mm in diameter and 8.5 mm in length, which is similar to commercially available TLD rods. The sensitive volume is located centrally and measures 1.5 mm in diameter and 6.0 mm in length; a portion 1.5 mm in diameter and 1.25 mm in length at each end is not used for dosimetry. The dispersion of response among dosimeters is small (coefficient of variation [ratio of the standard deviation to the mean] = 0.82%), and the reproducibility of repeat measurements by a single element is excellent (coefficient of variation = 0.29%), being superior to that of commercially available TLDs (10). Moreover, handling of the RPLGD is easier than for TLDs. A reader (FGD-1000, Chiyoda Technol, Tokyo, Japan) stimulates the RPLGD using a pulsed ultraviolet laser. Differences in fluorescence decay time between surface contamination (0.3 μs) and radiophotoluminescence (3 μs) enable discrimination between signal arising from contamination with finger grease or mucus from that due to absorbed radiation dose (10, 15, 16); thus, the new detector can be easily inserted and removed manually into and out of vectors and can be applied to regions in close contact with mucus because it does not require the complex cleaning processes necessary for TLDs and early RPLGDs. The reader repeats measurements 10–50 times within a few seconds and averages the values to reduce random errors. The quantity of radiophotoluminescence of a RPLGD is compared with that of a standard detector within the reader that has been irradiated with a known dose; the readout is expressed in Gy. Readout range is 10 μGy to 10 Gy, extendable to 500 Gy with optional settings. These new capabilities, coupled with the inherent properties of RPLGDs, mean that the new dosimeter can be easily applied to *in vivo* dosimetry studies. A preheat process at 70°C for 30 min and a cooling process to room temperature are necessary before each reading for which immediate reading after irradiation cannot be achieved. The details of individual correction factors derived using 4 MV X-rays have previously been described (12). For the 100 RPLGDs used in the current study, the coefficient of variation was 1.41% for dispersion among detectors, and the mean coefficient of variation for three-time repeat measurement was 1.29%. The linear dose response for RPLGD ($r = 1.000$, $p < 0.01$) for 1 to 136 Gy has been confirmed in our previous study (12).

Table 1. Patient characteristics

Age	Median 64 (35–81)
Sex	Male 30, female 36
Follow-up	Median 30 (1~58) months
Primary site	
Prostate	26
Gynecological	35 (previously irradiated 11)
Miscellaneous	5 (previously irradiated 1)
Total	66

RPLGD Vectors

Three types of vectors were developed for this study. Type 1 is a single "RPLGD complex", which was loaded to a 1.5-mm-deep slot carved on the upper part of the vaginal cylinder or on the perineal side of the template and was covered with gum paint (Fig. 1a); the RPLGD was located centrally, with a ø1-mm lead ball placed at each end as a radio-opaque marker. A 1-mm-long urethane spacer was placed between the RPLGD and each lead ball to avoid scratching. The Type 2 vector, used for the urethra, comprised a train of 10 "RPLGD complexes" loaded in a ø2-mm Teflon tube (Figs. 1b and 1c). The Type 3 vector, dedicated to the rectum, used a ø4-mm Teflon tube into which a train of 10 "encapsulated RPLGD complexes" was loaded manually; each RPLGD was contained in a plastic capsule to avoid excessive contamination by mucus (Fig. 1d). Three nylon threads were sutured to each end and to the midportion of the vector for fixation to the rectum.

Implantation

Implantation was performed in a lithotomy position under general and epidural anesthesia with or without spinal anesthesia. Before implantation, the Type 3 vector was sutured to the anterior rectal wall through a rigid rectoscope (Figs. 2a, 2b, and 2c). The entire vector length was kept in contact with the mucosa using at least three stitches; additional sutures were used if the vector was not in full contact with the mucosa. A median of 18 metal needles (range, 5–29) were implanted using a perineal template. Implant geometry was preplanned to cover the clinical target volume (CTV) with 85% basal dose isodose surface (BDIS) following the extrapolated Paris System to more than two-plane implants (17). Needle placement was guided by palpation and transrectal/vaginal ultrasound. For female patients, the vaginal cylinder was attached perpendicular to the template (Figs. 2a and 2b). The vaginal cylinder and metal needles were fixed to the template using screws and a template cap such that they were unified as a group and could only move