Table IV. Correlation coefficient among factors analyzed.

	Margin status	RT	HR[a]	T stage[b]	N stage[b]	Stage[b]
Margin status						
CC[c]	1	0.009	0.038	0.274	0.094	0.229
P-value		0.748	0.192	0	0.003	0
N[d]	1390	1373	1185	952	963	953
RT						
CC	0.009	1	0.051	0.037	0.066	0.093
P-value	0.748		58.058	0.245	29.029	3.003
N	1373	1722	1397	987	1086	1033
HR						
CC	0.038	0.051	1	0	0.025	0.042
P-value	0.192	0.058		0.991	0.447	0.204
N	1185	1397	1424	876	947	914
T stage[b]						
CC	0.274	0.037	0	1	0.201	0.733
P-value	0	0.245	0.991		0	0
N	952	987	876	987	986	987
N stage[b]						
CC	0.094	0.066	0.025	0.201	1	0.785
P-value	0.003	0.029	0.447	0	_	0
N	963	1086	947	986	1086	987
Stage[b]						
CC	0.229	0.093	0.042	0.733	0.785	1
P-value	0	0.003	0.204	0	0	
N	953	1033	914	987	987	1033

[a]Hormone responsiveness. [b]General Rules for Clinical and Pathological Recording of Breast Cancer (13th edition). [c]Pearson's correlation coefficient. [d]Number of available data.

Table V. Multivariate analyses.

	RR	95% C.I.	P-value
Margin status	1.183	0.898-1.557	P=0.231
Radiation therapy	0.227	0.168-0.307	P=0.000
T stage	1.293	1.009-1.655	P=0.042
N stage	1.867	1.508-2.312	P=0.000
Hormone receptor status	0.796	0.615-1.029	P=0.082

Number of available data: 848.

women >70 years of age who have early, estrogen-receptor-positive breast cancer with tamoxifen alone, rather than RT and tamoxifen, because the benefit of RT is still significant but very small (22). Thus, a subgroup of patients who have little or no benefit from RT has not been well defined yet. In Japan, however, whether to give RT after BCS remains controversial. Unfortunately, information regarding why RT was not given was not collected in this study; therefore, it cannot be rejected that a fear of radiation, which is characteristic of Japanese patients, caused them to decline RT, but it is more likely that the presiding surgeons did not offer RT because they believed that the patient's risk of IBTR was low enough to omit RT or that the benefit of RT did not exceed its harm. Consequently, the subjects in this study might have a bias that patients who did not receive RT had an apparently lower risk of IBTR than patients who actually received RT. Therefore, the observed result that the ratio of patients who received RT was significantly lower in patients who eventually had IBTR duplicated existing clinical evidence. In addition, previous meta-analyses suggested that the addition of RT after BCS significantly improved overall survival (5,23). Although the rationale for this observation was not fully explained, it is speculated that reduction of loco-regional recurrence leads to reduction of secondary dissemination to distant sites (23). Thus, omission of RT especially in young patients or patients with a high risk of IBTR, may deteriorate survival. Another interesting finding in this study is that the risk of IBTR is fairly constant over

more than 10 years for both patients who received RT and who did not. Regular check-ups for IBTR may be necessary after 10 years.

Regarding the characteristics of IBTR, 68.6% occurred within or adjacent to the original tumor bed, which is similar to existing observations (16,24,25). Of note, IBTR was salvaged with partial mastectomy in 48.6%. Although data are sparse regarding the method of salvage surgery, partial mastectomy, which is equivalent to breast-conserving salvage surgery, seems higher than in existing studies (26-29). This might be related to the fact that 29% (148/505) of patients had not received RT as initial treatment and RT can be administered safely after salvage surgery.

This study has several limitations. Almost all patients who developed IBTR in participating institutes were registered in this study; however, the completeness of registration for patients who did not develop IBTR is unknown in some institutes. Moreover, information regarding systemic adjuvant therapy and the details of RT were not collected for each patient; therefore, substantial bias may exists regarding systemic therapy and/or the radiation dose to the tumor bed between patients who had IBTR and patients who did not. This might have been why the margin status and young age, both of which are well known risk factors for IBTR, did not have a significant impact in this study. In other words, patients with unfavorable tumor factors who had RT may have had a better outcome than patients without unfavorable tumor factors who did not have RT. In conclusion, the results shown in this study, together with existing evidence, indicate that omission of RT after BCS is the most significant treatment factor related to IBTR. RT should be offered as standard for all patients who undergo BCS. Deterioration of local control and, possibly, overall survival should be discussed with patients before offering to omit RT.

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Questionnaire Survey of Treatment Choice for Breast Cancer Patients with Brain Metastasis in Japan: Results of a Nationwide Survey by the Task Force of the Japanese Breast Cancer Society

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Objective: A nationwide survey was performed to investigate the current patterns of care for brain metastasis (BM) from breast cancer in Japan.
Method: A total of 351 survey questionnaires were sent to community or academic breast oncologists who were members of the Japanese Breast Cancer Society as of December 2005. The questionnaire consists of 40 multiple choice questions in eight categories.
Results: Of 240 institutions sent survey questionnaires, 161 (67.1%) answered; 60% of institutions answered with '<5' patients with BM every year; almost half (83 of 161) screened for BM in asymptomatic patients; surgical resection was rarely performed, as ~75% of institutions (118 of 160 institutions) answered 'none or one case of surgery per year'; 27% (41 of 154) preferred stereotactic radiosurgery (SRS) over whole-brain radiotherapy (WBRT) as the initial treatment in all cases, although ~70% (100 of 154) of them answered 'depend on cases'. The preference for SRS over WBRT mainly depends on the impressions of breast oncologists about both safety (late normal tissue damage and dementia in WBRT) and efficacy (better local control by SRS). Eighty-one percent (117 of 144) of institutions did not limit the number of SRS sessions as far as technically applicable.
Conclusion: SRS is widely used as the first choice for BM from breast cancer in Japan. Considerable numbers of Japanese breast oncologists prefer SRS over WBRT as the initial treatment for BM. A randomized trial comparing SRS and WBRT is warranted.

Key words: breast cancer – brain metastasis – stereotactic radiosurgery – whole-brain radiotherapy

INTRODUCTION

Brain metastasis (BM) is one of the most devastating complications of cancer and is usually associated with poor prognosis. The incidence of BM is high among patients with breast cancer, 10–20% in general (1). The incidence of BM in patients with HER2/neu over-expression is considered to be especially high, around 25–40% (2–5).

Whole-brain radiotherapy (WBRT) is the standard treatment for most patients with BM. For patients with a single BM, surgery followed by WBRT is superior to WBRT alone (6,7), although some studies does not support this (8). For patients with limited number (usually one to three) of BM, there is a controversy as discussed later (9). For patients with multiple (usually four or more) BM, WBRT is standard treatment.

Stereotactic radiosurgery (SRS) was developed in 1950s (10) and is now widely used as an alternative to surgery, WBRT and sometimes both. WBRT followed by SRS boost

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has also been studied (11,12) and is considered a standard treatment for patients with a single metastasis. Radiation-induced necrosis, especially after WBRT, is a rare but irreversible complication (13), which leads to the frequent use of SRS for the treatment of BM.

Withholding WBRT, SRS alone as upfront therapy is thought to be an alternative to BM (14–17). One prospective study compared SRS alone with SRS plus WBRT (18), which did not show a statistically significant difference in terms of overall survival. A relatively small sample size, decreased local control rate and lack of difference in neurological adverse events made it difficult to conclude that SRS alone was not inferior to SRS plus WBRT (19). Although this evidence confirms WBRT as standard treatment, SRS alone is widely used in daily practice.

BM in breast cancer is unique, compared with BM in other primaries, for certain reasons. The first is the high incidence of BM in breast cancer, especially in patients with the Her2/neu subtype, which has already been mentioned. The second is, BM in breast cancer is more radiosensitive than that in other primary such as non-small cell lung cancer or renal cell carcinoma. This may lead to better local control of BM by WBRT only. The third is the better prognosis after diagnosis of BM, especially in patients with Her2/neu positive subtype (20). This may lead to increased concern about radiation necrosis and failure of local control. For these reasons, BM in breast cancer is unique in terms of risk-benefit balance. A prospective trial, ideally exclusive to breast cancer, is needed for optimal usage of SRS.

As preparation for a future prospective trial, the task force of the Japanese Breast Cancer Society made a questionnaire survey of treatment choices for breast cancer patients with BM.

PATIENTS AND METHODS

A total of 351 survey questionnaires were sent to community or academic breast oncologists who were board members of the Japanese Breast Cancer Society, in December 2005. For most institutions, one breast oncologist was selected from each institution. For some large institutions, two or more oncologists were selected, because they have multiple hospitals or divisions that may have different treatment strategies. To avoid duplicated answers from the same treatment team, we attached the statement asking to unite one answer from one hospital or divisions. The questionnaire consists of 40 multiple choice questions in about eight categories, such as characteristics of hospitals, screening for BM, operation, radiation, re-irradiation, chemotherapy, SRS and cost.

RESULTS

Of 240 institutions to which we sent survey questionnaires, 161 (67.1%) answered. More than 90% of answers were obtained from surgical oncologists; the remainders were radiation and medical oncologists, reflecting the current situation that most patients with breast cancer are treated by surgeons in Japan. The background characteristics of each institution are summarized in Table 1. Both small and large institutions were included in this survey. In many institutions, BM was a rare complication (60% of institutions answered '<5' patients with BM every year), but some institutions treat many BM patients (>20 patients per year). In 75% (125 of 155) of institutions, the treatment decision is made by a neurosurgeon and/or radiation oncologist.

More than half the institutions (83 of 161) screened for BM, although no evidence exists to support a screening strategy (Table 2). Timing of screening for BM differed, although more than half of the institutions with a screening strategy screen at disease progression. Some institutions screened before starting trastuzumab.

Table 1. Characteristics of each institution

Characteristics	Category	Number	%
Number of new patients/year	1–50	34	21
	51–100	57	35
	101–150	30	19
	151–200	15	9
	201 over	25	15
Number of new BM/year	<5	95	60
	6–10	47	29
	11–20	13	8
	21 over	5	3
Radiation oncologist in your hospital?	Yes	121	75
	No	40	25
Stuff neurosurgeon in your hospital?	Yes	131	82
	No	29	18
Treatment decision mainly made by	Neurosurgeon	71	46
	Breast oncologist	40	25
	Radiation oncologist	32	21
	Conference	12	8

BM, brain metastasis.

Table 2. Screening

Question	Answer	Number	%
Screening for BM	Yes	83	52
	No	78	48
If yes, when?	At systemic progression	48	58
	Routinely	18	21
	Before Trastuzumab	9	11
	Other conditions	8	10

Surgical resection was less frequently used as local therapy for BM because ~75% of the institutions (118 of 160) answered 'none or one case who received surgical resection per year'' (Table 3). The infrequent choice of surgical resection might be a result of the rigid indications for surgery. More than 60% of institutions answered that no evidence of systemic disease except for BM, or controlled systemic disease by systemic therapy was crucial for surgical resection. WBRT, not SRS, was dominantly used for postoperative radiotherapy.

The indication for WBRT is summarized in Table 4. Different from surgical resection, it was not dependent on prognosis (87% of institutions answered that they considered radiotherapy regardless of the prognosis, for symptom relief). Even in patients with a poor performance status, WBRT can be used. More than 30% of institutions (52 of 161) answered that they would consider WBRT for patients with ECOG PS 4, if clinically needed. Eighty-one percent of institutions (124 of 154 institutions) interrupted chemotherapy during WBRT, although some institutions did not.

Table 5 summarizes the questions about re-irradiation for patients who had progressed to BM after WBRT. More than 80% of institutions answered that they did not repeat radiotherapy except for SRS. Interval as an indication for re-irradiation is controversial. Sixteen institutions needed an interval before re-irradiation, whereas another 14 institutions did not. Regarding the risk of re-irradiation, most surgeons estimated that the risk was greater than a few percent, but did not present their estimate to patients numerically.

Table 6 summarizes the questions about SRS and cost. Only 7% (13 of 154) of institutions gave WBRT as their first choice, although ~70% (100 of 154) answered 'depend on cases'. The indication for SRS according to the metastatic site, size and the number of BMs largely influenced the treatment decision. Concerning the indication for SRS, 98% (98 of 100) of institutions limited SRS for only small (<3 cm) lesions. Seventy-one percent (76 of 108) of institutions choose SRS only for patients with a limited number (<5 lesions) of BMs. However, 81% (117 of 144) of institutions did not limit the number of sessions as long as neurosurgeons technically permitted SRS. There was no consensus concerning prognosis and PS as indications for SRS. SRS was preferred to WBRT for both safety (less dementia) and efficacy (better BM control) reasons. The cost of SRS was not precisely estimated by the majority of surgeons.

Table 3. Operation

Question	Category	Number	%
BM surgery cases/year	0–1	118	74
	2–5	37	23
	6–9	3	2
	10 or more	2	1
Indication for surgery	NED other than BM	55	32
	Stable systemic disease	53	31
	Prognosis more than 6 months	15	9
	Regardless of prognosis, if symptoms treatable only by surgery	48	28
Post-surgery radiation	WBRT	102	69
	SRS	45	31

NED, no evidence of disease; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery.

Table 4. Radiation

Question	Category	Number	%
Indication for RT	Prognosis	22	14
	Symptom improvement	136	84
	Upon request	3	2
PS	Only 0–2	53	33
	Only 0–3	56	35
	Regardless of PS, if communicable	39	24
	Regardless of communication, upon situation	13	8

RT, radiotherapy; PS, performance status.

Table 5. Repeat radiation

Question	Category	Number	%
Re-RT after WBRT?	Never	41	26
	Only SRS	94	58
	SRS or Local Rt	21	13
	If indicated, WBRT	5	3
For indication of repeat radiation (local RT or WBRT), does interval from first WBRT matter?	Yes (some interval needed)	16	53
	No	14	47
If you repeat radiation (SRS, local RT, WBRT), how do you tell patients about the risk of necrosis?	Will not tell	9	8
	Will tell, but not numerically	66	60
	<1%	0	0
	'a few percentage'	19	17
	'ten and a few %'	12	10
	'20–40%'	5	5

DISCUSSION

This survey revealed that SRS is widely used as the first choice for BM treatment for patients with breast cancer in Japan. Many Japanese breast oncologists prefer SRS to WBRT as radiation therapy against BM. There are

Table 6. Stereotactic radiosurgery

Question	Category	Number	%
First choice of RT for BM	SRS	41	27
	WBRT	13	8
	Depends on cases	100	65
If you answer 'depends on cases', depends on what?	Maximum size	70	
	Number of BM	100	
	Location of BM	45	
	Control of systemic disease	18	
	PS	28	
	Financial status and others	8	
Maximum size for SRS	<2 cm	30	27
	<2.5 cm	12	11
	<3 cm	66	60
	<4 cm	2	2
Maximum number of BM for SRS	Only single	3	3
	2–4	73	68
	5–10	18	16
	No limitation in number	14	16
How control of systemic disease influences choice of RT for BM?	If good control, SRS	12	43
	If poor control, SRS	16	57
How prognosis influences choice of RT for BM?	SRS for poor prog.	7	21
	SRS for better	11	32
	Any prog. If PS is good	16	47
How many times will you repeat SRS	Only once	6	4
	Twice	15	10
	Three times	6	4
	No limitation in number	117	82
What is the main reason you avoid WBRT?	Hair loss	8	10
	Dementia	29	35
	Long treatment	16	19
	Worse BM control	30	36
Experience of neurological disturbance after WBRT	Yes	39	27
	No	107	73
Do you know the cost of WBRT exactly?	Yes	25	14
	No	120	86
Do you know the cost of SRS exactly?	Yes	27	19
	No	116	81

discrepancies between NCCN guideline recommendations and the practice in Japan. For example, for a limited number of BM, 30% of Japanese breast oncologists use SRS as adjuvant treatment although NCCN guidelines recommend WBRT as adjuvant treatment after surgery. For multiple BM, 30% of Japanese breast oncologists use SRS for patients with more than five BM, although NCCN guidelines recommend WBRT. For both a limited number of, and multiple, BM 60% of Japanese breast oncologists use SRS, although NCCN guidelines recommend WBRT for patients with systemic disease refractory to aggressive treatment. What causes these discrepancies, a preference for SRS and reluctance to use WBRT? Our survey revealed that Japanese breast oncologists believe that SRS is a safer and more effective treatment than WBRT, as shown in Table 6. Interestingly, one of the major concerns about WBRT was dementia, although 70% had not actually experienced it. Nonetheless, they did not limit the number of sessions for SRS. It seems that they believe that SRS is much safer than WBRT. Lack of recognition of the precise cost of SRS also enhances this preference for SRS, because the current national insurance system covers 70–90% of the total costs of SRS, which costs 500 000 yen per session.

The present study suggests issues for future trials. First, as shown in Table 1, the treatment decision for BM is shared by neurosurgeons and radiation oncologists, so their collaboration is essential. Another suggestion is the consideration of screening. More than half of the institutions had screened for BM although there is no supporting evidence. This should be taken into account when designing a clinical trial because screening may detect BM earlier in its clinical course, influencing the treatment choice (fewer lesions may lead to more SRS) and the survival of BM patients as a result of lead-time bias. Preference for SRS and its reasons are also important. A future trial on SRS should answer two questions: first, is limitless repetition of SRS safer than WBRT in terms of the long-term adverse effects of radiotherapy? and second, is SRS superior to WBRT in terms of local control? To answer these two questions, we need a prospective trial comparing WBRT with SRS for patients with breast cancer having limited number, and small size, of BM. This kind of randomized study would need too large a sample size to be conducted in Japan only, so international collaboration would be needed.

One limitation of the present study is that a questionnaire from one oncologist at an institution does not demonstrate the pattern of practice at the institution perfectly, because there could be many biases such as recall bias, response bias and so on. Although the background of institutions shown in Table 1 seems to show that this survey describes the current pattern of practice in Japan well, actual data from each institution are more helpful. We have therefore planned a historical cohort study to reduce these biases.

In conclusion, the present study showed that SRS alone is widely used as BM treatment for patients with breast cancer in Japan. To address the issues of both safety and efficacy, a future prospective trial studying the optimal usage of screening, SRS and WBRT is warranted.

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Conflict of interest statement

None declared.

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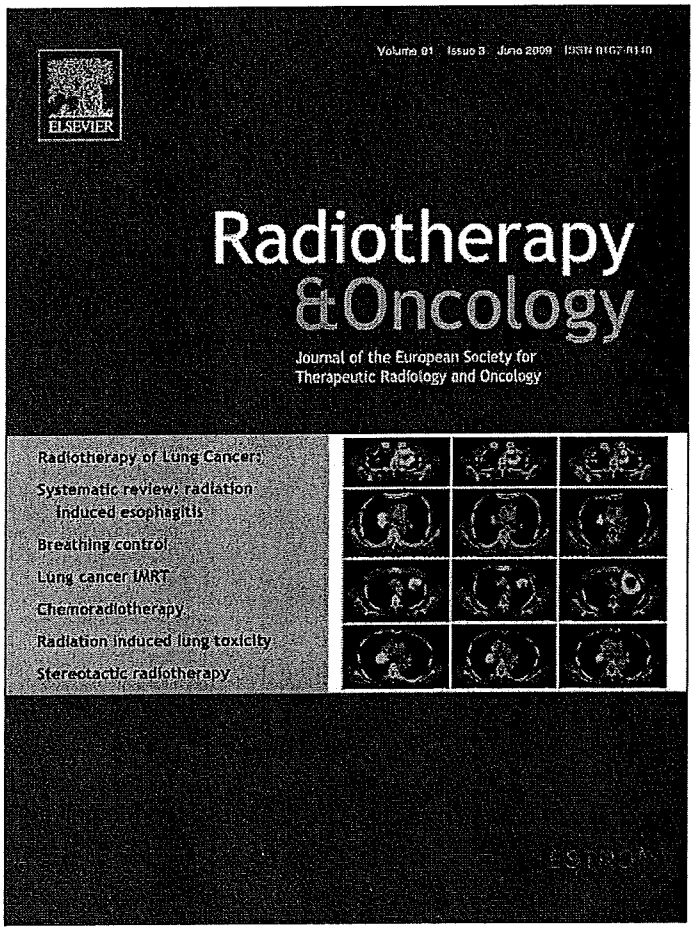

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Lung cancer RT

Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses

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ABSTRACT

Introduction: The role of elective nodal irradiation of non-small-cell lung cancer (NSCLC) patients treated with radiotherapy remains unclear. We investigated the significance of treating clinically uninvolved lymph nodes by retrospectively analyzing the relationship between loco-regional failure and the irradiated volume.

Methods: Between 1998 and 2003, patients with IA–IIIB NSCLC were treated with radiotherapy. The eligibility criteria for this study were an irradiation dose of 60 Gy or more and a clinical response better than stable disease. Typical radiotherapy consisted of 40 Gy/20 fr to the tumor volumes (clinical target volume of the primary tumor [CTVp], of the metastatic lymph nodes [CTVn], and of the subclinical nodal region [CTVs]), followed by off-cord boost to CTVp+n to a total dose 60–68 Gy/30–34 fr. The relationship between the sites of recurrence and irradiated volumes was analyzed.

Results: A total of 127 patients fulfilled the eligibility criteria. Their median overall and progression-free survival times were 23.5 (range, 4.2–109.7) and 9.0 months (2.2–109.7), respectively. At a median follow-up time of 50.5 months (range, 14.2–83.0) for the surviving patients, the first treatment failure was observed in 95 patients (loco-regional; 41, distant; 42, both; 12). Among the patients with loco-regional failure, in-field recurrence occurred in 38 patients, and four CTVs recurrences associated with CTVp+n failure were observed. No isolated recurrence in CTVs was observed.

Conclusions: In-field loco-regional failure, as well as distant metastasis, was a major type of failure, and there was no isolated elective nodal failure. Radiation volume adequacy did not seem to affect elective nodal failure.

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Radiation therapy is an integral component of the multi-modal treatment of non-small-cell lung cancer (NSCLC). Recent phase III studies have demonstrated that concomitant chemoradiotherapy improves survival, and this has resulted in the general acceptance of concurrent chemoradiotherapy as one of the standard treatments for locally advanced NSCLC [1]. Despite the improved survival, however, most patients die from their disease as a result of local or distant failure.

Local failure remains a major challenge when treating NSCLC with radiotherapy. A number of studies of dose escalation to the gross tumor volume (GTV) have been conducted as a means of improving local control [2–5]. The conventional radiation fields for NSCLC typically encompass the entire mediastinum and ipsilateral hilum (elective nodal region) to deliver a dose of 40 Gy, even without evidence of disease in these areas, followed by a 20 Gy boost to the GTV. However, the conventional treatment has added considerable morbidity and can limit the dose escalation. In phase I–II dose escalation studies, there is a trend toward omitting the practice of elective nodal irradiation (ENI) after their experiences with toxicity, which is not based on direct evidence [2–5]. According to those studies, omitting ENI has not sacrificed treatment outcomes so far. They also analyzed patterns of recurrence in relation to irradiated volume in a dose escalation setting [6].

By contrast, the current literature provides limited information regarding patterns of failure when conventional fields and doses are used [7,8]. Since it is important to know whether loco-regional failure is within or outside the irradiation field, we retrospectively analyzed patterns of failure after radiation therapy for NSCLC, especially in regard to the relationship between local failure and irradiated volume.

Methods and materials

Patients

Between January 1998 and March 2003, 263 patients with newly diagnosed NSCLC were treated with thoracic radiation therapy,

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with or without chemotherapy, at the National Cancer Center Hospital. All tumors were cytologically or histologically confirmed NSCLC. Patients' disease was staged by the tumor-node-metastasis (TNM) staging system (UICC, version 6, 2002). The diagnostic workup included a bone scan, brain scan by computed tomography (CT) or magnetic resonance imaging, CT scan of the chest, and CT or ultrasound imaging of the abdomen. The criteria for inclusion in this study were irradiation with a dose of 60 Gy or more as a part of the initial treatment and a clinical response better than stable disease. After excluding patients with metastatic disease, whose primary tumor was located in the apex of the lung (superior sulcus), and whose post-treatment evaluation was inadequate, the remaining 127 patients served as the subjects of the analysis.

Details of treatment

Radiotherapy

Gross tumor volume (GTV) was defined as the demonstrable extent of the primary tumor and the metastatic lymph nodes, GTVp and GTVn, respectively. GTVn was defined as abnormally enlarged regional lymph nodes measuring over 1.0 cm along their short axis. Clinical target volume (CTV) consisted of the adjacent mediastinum and ipsilateral hilum (CTV of the subclinical nodal region, CTVs) as well as CTVp and CTVn which were assumed to be equal to GTVp and GTVn, respectively. A planning target volume (PTV) margin of 1–1.5 cm was drawn around each CTV.

External-beam radiotherapy with a 6, 10, or 15 MV photon beam was delivered using a linear accelerator. A majority of the patients were treated with anteroposterior opposing fields encompassing CTV to a dose of 40 Gy/20 fractions (2 Gy per fraction, 5 days per week), followed by an off-cord boost to the GTV by oblique opposing fields, to a total dose of 60–68 Gy/30–34 fractions. No attempt was made to encompass the supraclavicular areas in most patients; the supraclavicular areas were treated only electively. Initially, treatment planning was performed by using an X-ray simulator for the anteroposterior fields and a CT-port for the oblique opposing fields, but after the end of 1999, most treatment planning, especially to define the off-cord boost, was performed using a CT-based planning system (FOCUS, Computed Medical Systems).

The dose to the spinal cord was limited to 45–50 Gy. The size of the treatment fields was adjusted so that it did not exceed half of the hemithorax before introducing CT-based planning system, or so that the volume of normal lung tissue receiving a dose over 20 Gy would be less than 40%.

Chemotherapy

Systemic chemotherapy was used in 87 patients (68.5%), and the majority of the patients received platinum-based chemotherapy sequentially or concurrently with the radiation therapy. One of the representative regimens was 2–3 cycles of cisplatin 80 mg/sqm on day 1 and vinorelbine 25 mg/sqm on days 1 and 8 (or vindesine 3 mg/sqm on days 1, 8, and 15) in 21–28 days. The second most common regimen was cisplatin 80 mg/sqm on day 1, vindesine 3 mg/sqm on days 1 and 8, and mitomycin C 8 mg/sqm on day 1, in 21–28 days. The other regimens are summarized in Table 1.

Evaluation

Patients were followed at 4- to 6-week intervals for 6 months after treatment and at 3- to 6-month intervals thereafter. Chest X-ray and laboratory workups were performed at each post-treatment visit. Unless there were changes in the chest X-ray or in symptoms, a CT scan was performed about 2–3 months after the treatment for the assessment of the treatment response, and every 6–12 months thereafter. Follow-up information was obtained from the medical charts and death certificates.

Table 1
Baseline patient characteristics.

Characteristics	Patients	(%)
Median age (yr)	65 (36–83)	
Gender		
Male	106	83
Female	21	17
Performance status (WHO)		
0	12	9
1	109	86
2	6	5
Stage		
I (A/B)	5(1/4)	4
II (A/B)	12(3/9)	9
III (A/B)	110(59/51)	87
Histology		
Adenocarcinoma	64	50
Squamous cell carcinoma	39	31
Large cell carcinoma	4	3
NSCLC (not otherwise specified)	20	16
Chemotherapy (concurrent/sequential)	87(63/24)	69
Chemotherapy regimens		
Cisplatin + vindesine or vinorelbine	48	55
Carboplatin + paclitaxel	12	14
MVP (cisplatin + vindesine + mitomycin)	12	14
Nedaplatin or nedaplatin + paclitaxel	11	13
Others	4	5

When evaluating overall survival, an event was defined as death from any cause. When evaluating progression-free survival, an event was defined as documented tumor progression (loco-regional or distant) or death from any cause. Local or loco-regional failure was judged to have occurred if there was radiographic evidence of progressive disease. Absence of progression of residual disease for more than 6 months following treatment was considered evidence of loco-regional control. A recurrence in supraclavicular nodes was considered regional failure, not an elective nodal failure, because the supraclavicular regions are not routinely included within the radiation fields in our practice. Treatment failure was not always confirmed histologically. Elective nodal failure (ENF) was defined as recurrence in CTVs without evidence of local failure, as the first event or even after distant metastasis.

The adequacy of field borders was assessed in terms of CTVs coverage and PTV margin in patients with loco-regional failure. The failure patterns were analyzed to distinguish in-field recurrence from out-of-field recurrence; "in-field" included CTVs as well as CTVp and CTVn.

The Kaplan–Meier method was used from the start of the treatment to calculate the overall survival and progression-free survival of all the 127 patients.

Results

A total of 127 patients, median age 65 years (range, 36–83), met the criteria for evaluation in this study. The majority of patients had stage IIIA ($n = 59$) or IIIB ($n = 51$) disease. Other baseline characteristics of the patients and details of their treatment are summarized in Table 1.

At a median follow-up time of 50.5 months (range, 14.2–83.0) of the surviving patients, 95 had experienced treatment failure. Median survival time was 23.5 months (range, 4.2–109.7), and median time to progression was 9.0 months (range, 2.2–109.7). The 2-year cumulative survival rate and 2-year progression-free survival rate were 51.4% and 27.6%, respectively. The survival

curves are shown in Fig. 1. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Eighty-seven (69%) patients received chemotherapy concomitantly or sequentially with the radiotherapy. The overall survival time of the patients who received chemotherapy was 21.7 months (range, 7.6–33.9), as opposed to 19.1 months (range, 6.8–32.7) among those who did not receive chemotherapy, and the difference was not statistically significant ($p = 0.10$). There were no statistically significant differences in disease-free survival nor loco-regional control according to whether the patients had received chemotherapy. Concurrent use of chemoradiotherapy did not affect survival among the 87 patients who received chemotherapy (data not shown).

There were 53 patients with a first loco-regional failure, alone ($n = 41$) or with distant metastasis ($n = 12$), and the majority of the failures were in-field ($n = 38$, 72%). Nine (21%) patients had out-of-field recurrences in the form of supraclavicular node metastasis ($n = 5$) or pleural metastasis ($n = 4$), with or without local recurrence. There were no isolated ENFs (Table 2).

Four patients (7%) experienced nodal failure in CTVs simultaneously with local or distant failure. Three of them had received a prophylactic dose of 40 Gy to the CTVs, and the other had inadequate margin of the CTVs field. Other characteristics of these patients are shown in Table 3. There were no "marginal only" failures among in-field failures; all the failures at the field borders were associated with out-of-field failures.

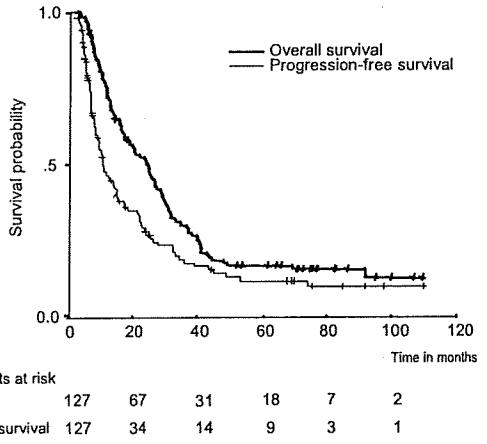

Fig. 1. Overall and progression-free survival curves of all the 127 patients. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Table 2
Details of all the first failures.

Types of event	Patients	%
Loco-regional alone	41	43%
In-field		
CTVpn	30	
CTVpn + CTVs[a]	2	
In-field + out-of-field		
CTVpn + pleural effusion	2	
CTVpn + supraclavicular nodes	2	
Out-of-field		
Supraclavicular nodes	3	
Pleural effusion[b]	2	
Loco-regional + distant	12	13%
In-field + out-of-field		
CTVpn + CTVs	2	
Distant alone	42	44%
All events	95	

[a] One also had concurrent failure in the contralateral hilum.
[b] One also had concurrent supraclavicular recurrence.

Conventional X-ray simulation was performed in 8 (6%) patients, while 70 (55%) had CT-based simulation and remaining 49 (39%) had both (initially with X-ray simulation, followed by CT-based simulation for off-cord boost). A majority ($n = 122$, 96%) of the patients were treated with anteroposterior opposing fields as elective nodal irradiation, followed by oblique opposing fields to the total dose.

ENI was incomplete ($n = 12$) or not performed ($n = 6$) in 18 of the 53 patients with loco-regional failure because of diminished pulmonary function or deteriorated performance status. All the incomplete ENIs were due to insufficient CTVs coverage. In 12 of the 18 patients, the failure was in the tumor volume, in 3 patients it was in the pleura, and in 2 patients it was in the supraclavicular nodes. Only 1 patient had recurrence in both the tumor volume and the uninvolved nodal area.

Discussion

In this series of NSCLC cases treated with conventional fields and doses, the loco-regional failures after radiotherapy mainly occurred in the tumor volumes, and there were no isolated ENFs.

There are several possible reasons for these results. First, micrometastasis in the CTVs may have been controlled by prophylactic delivery of 40 Gy to the region, and depending on the location of the primary tumor, the sites of occult metastasis may often have received additional unintentional radiation doses. Kepka et al. reported an isolated ENF rate of 9% in 185 patients treated with the ENI using 3-dimensional conformal radiotherapy (3D-CRT). Their analysis showed that the ENF occurred more frequently in the regions that received under 40 Gy than in the regions that received higher doses (69% vs. 31%, respectively, $p = 0.04$) [7]. However, despite the same ENF rate of 9% in 1705 patients in the four trials conducted by the Radiation Therapy Oncology Group (RTOG), a retrospective evaluation of in-field progression revealed that neither in-field progression nor survival was affected by the adequacy of ENI [8]. Field adequacy did not have any negative impact on regional control in our series either (Tables 3).

Second, the amount of micrometastasis in unenlarged mediastinal regional nodes may have been small enough to be controlled by chemotherapy, which has been shown to have activity that reduces the incidence of distant micrometastasis in advanced NSCLC. However, the degree of systemic and local efficacy of chemotherapy did not reach statistical significance in our series, probably because of the small number of patients and their heterogeneity (data not shown).

Third, since the failure sites in the majority of patients were distant, they would have died of their disease before the ENF became apparent. As a result, the loco-regional failure rates may have been lower than their true values because we did not investigate regional sites once a patient developed distant metastasis.

The therapeutic significance of treating subclinical nodal regions during and after surgery for NSCLC has been questioned. Some studies have established the presence of considerable microscopic nodal disease in clinically uninvolved lymph nodes [9,10], but the role of mediastinal lymphadenectomy remains controversial and has been limited to the precise staging of the disease [11–13]. A study by Izbicki et al. which compared systemic mediastinal lymphadenectomy with mediastinal lymph node sampling showed that radical systemic mediastinal lymphadenectomy had no effect on the disease-free or overall survival of patients with limited nodal involvement [13,14]. The role of adjuvant radiotherapy after complete resection also remains unclear [15–17]. A systemic

Table 3
Patients with CTVs failure.

	Patient #1	Patient #2	Patient #3	Patient #4
Age (yr)/Sex	45/Female	74/Female	61/Male	78/Male
Reason for inoperability	Unresectable	Unresectable	Decreased pulmonary function	Unresectable, age
Stage	IIIA	IIIA	IIB	IIIB
Primary location	Left lower lobe	Right upper lobe	Right lower lobe	Left upper lobe
Histology	Adenocarcinoma	Adenocarcinoma	Squamous cell carcinoma	Adenocarcinoma
Chemotherapy	Yes	Yes	No	No
Response	Partial response	Partial response	Partial response	Partial response
Site of first failure	Distant and loco-regional	Distant and loco-regional	Loco-regional	Loco-regional
Field border adequacy	Yes	Yes	No	Yes
Dose to CTVs failure	40	40	0	40
Death	No	No	Yes	No

review and meta-analysis [18] showed that postoperative radiotherapy was detrimental to patients with early NSCLC, although there may have been some efficacy in patients with N2 tumors. These arguments also raise questions about the clear benefit of ENI in regard to survival.

In-field loco-regional failure was a major site of failure in the current study: all the recurrences in the CTVs were associated with failure in the gross tumor volume. Thus, more intensive treatment strategies are needed to enhance loco-regional control without sacrificing safety. One possible strategy is to reduce the ENI field in regard to the patients' risk factors while escalating the total dose. Such an attempt has already been made in regard to surgery: Asamura et al. retrospectively reviewed the prevalence of lymph node metastasis with respect to the location of the primary tumor or other characteristics to decide on the optimal lobe-specific extent of systematic lymph node dissection for NSCLC [19,20]. By using such predictors, including the location of the primary tumor, histology, or nodal stage [21–24], it is possible to identify the nodal areas at risk and to optimize the extent of ENI in radiation therapy as well. On the other hand, more precise diagnosis by novel technology, such as positron emission tomography [25], may enable the omission of ENI and avoid unnecessary irradiation to areas at low risk for subclinical disease.

In terms of the technical feasibility of dose escalation, Grills et al. found that intensity-modulated radiation therapy without ENI for NSCLC increased the deliverable mean target dose in node-positive patients by 25–30% over 3D-CRT and by 130–140% over traditional ENI [26].

Because omitting ENI is likely to leave microscopic disease untreated, there is concern that it may result in increased failure in these areas. However, the preliminary results of dose escalation trials have shown that isolated ENF outside the irradiated volume occurred in fewer than 6% of the cases and that omission of ENI did not seem to sacrifice outcome [2–5,27]. There is insufficient evidence to support the use of ENI for any patient with localized NSCLC (Stages I–III), irrespective of whether chemotherapy is administered [28]. There has been only one randomized trial that compared high-dose thoracic radiotherapy without ENI and standard dose radiotherapy with ENI, and it showed a survival benefit of high-dose thoracic radiotherapy without ENI [29]. One possible explanation for this finding is that incidental doses to elective nodal areas may contribute to the eradication of the subclinical disease. The pattern of ENF according to nodal regions was described by Rosenzweig et al., who implemented the use of involved-field radiation therapy with dose escalation in 524 patients [6]. Since the majority of the 42 ENFs that were observed occurred in the areas that received less than 45 Gy, the incidental doses to elective nodal areas may have been substantial despite the attempt not to treat these regions in their study. In addition, Zhao et al. reported that involved-field radiation therapy with a dose escalated to 70 Gy delivered a considerable dose to CTVs, and when the primary tumor was large or centrally located, the percentages of CTVs in the lower paratracheal region, subcarinal region and ipsilateral hilar region receiving over 40 Gy were 33%, 39%, and 98%, respectively [30].

Because of the retrospective nature of our study, no conclusions about the value of ENI for NSCLC can be drawn. However, the finding that in-field loco-regional failure, as well as distant metastasis, was a major type of failure with the standard field and dose of thoracic radiotherapy confirmed the need for more intensive treatment.

Further investigation to verify the true significance of ENI or to identify best candidates for ENI is necessary before it is abandoned in the context of dose escalation.

Conclusion

The loco-regional failures after radiotherapy in this series of NSCLC cases treated with conventional fields and doses mainly occurred in the tumor volumes, and there were no isolated ENFs. The results confirmed the need for more intense treatment to improve local control.

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Gender Difference in Treatment Outcomes in Patients with Stage III Non-small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy

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Objective: To identify any gender differences in the outcomes of concurrent platinum-based chemotherapy and thoracic radiotherapy for unresectable stage III non-small cell lung cancer (NSCLC).
Methods: A comparative retrospective review of the clinical characteristics and treatment outcomes between female and male NSCLC patients receiving chemoradiotherapy.
Results: Of a total of 204 patients, 44 (22%) were females and 160 (78%) were males. There was no difference in age, body weight loss, performance status or disease stage between the sexes, whereas never-smokers and adenocarcinoma were more common in female patients (55% vs. 3%, $P < 0.001$, and 73% vs. 55%, $P = 0.034$, respectively). Full cycles of chemotherapy and radiotherapy at a total dose of 60 Gy were administered to ~70% and >80% of the patients, respectively, of both sexes. Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$), but the median progression-free survival did not differ between the sexes. The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$).
Conclusions: This study failed to show any gender differences in the survival or toxicity among patients treated by concurrent chemoradiotherapy. These results contrast with the better survival in female patients undergoing surgery for localized disease or chemotherapy for metastatic disease.

Key words: gender – female – non-small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Lung cancer in women differs from that in men with respect to its incidence, association with smoking, and histological distribution (1). Several epidemiological studies have shown that female smokers have a 1.5- to 3-fold higher risk of developing lung cancer than male smokers, suggesting that women may have an increased susceptibility to the carcinogens in tobacco. Never-smokers with lung cancer are more likely to be female than male, and in East Asian countries, as high as 70% of the women diagnosed with lung cancer have never smoked in their lives. Women are more likely to develop adenocarcinoma than squamous cell carcinoma, the latter being more common in men. This difference cannot be explained fully by differences in the smoking patterns, and potentially suggests basic differences in the etiology of lung cancer between the sexes (1).

Prospective cohort studies and a large population-based study have consistently shown that female gender is a favorable prognostic factor in patients with non-small cell lung cancer (NSCLC). These studies, however, included patients

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with all stages of cancer, and the therapies administered are not specified (2–4). The existence of a gender difference in survival remains controversial among patients with locally advanced NSCLC receiving radiation-based treatment. Some studies have shown better survival in females than in males (5–7), whereas others have shown no difference in survival between the sexes (8,9). Many patients in these studies, however, received radiotherapy alone, which is no longer the standard treatment for locally advanced disease. Furthermore, all but one of these studies included patients with stage I–II disease who were considered unsuitable for surgical treatment because of poor general condition. One study that addressed gender differences in unresectable stage III NSCLC patients treated by chemoradiotherapy showed a median survival time in women of 19.7 months and in men of 21.7 months ($P = 0.26$) (10). The objectives of this study were to compare the outcomes of concurrent chemoradiotherapy between female and male patients with stage III NSCLC.

PATIENTS AND METHODS

Study Population

Patients with unresectable stage III NSCLC who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1994 and 2005 were eligible for this study. A total of 204 patients were identified. Patients treated by sequential chemotherapy and thoracic radiotherapy were excluded from this study, because we consider that the standard of care for unresectable stage III NSCLC without effusion is concurrent chemoradiotherapy, and sequential treatment is only given to patients in poor general condition or those with tumors too large for radiotherapy initially, which are expected to shrink sufficiently for radiotherapy after chemotherapy. All patients underwent a systematic pre-treatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, computed tomographic (CT) scans of the chest and abdomen, CT or magnetic resonance imaging of the brain, and bone scintigraphy. Chemotherapy consisted of cisplatin combined with either vinorelbine ($n = 125$), vindesine with or without mitomycin ($n = 46$), or other drugs ($n = 6$) repeated every 4 weeks, carboplatin and docetaxel ($n = 10$) administered weekly, and nedaplatin and paclitaxel administered every 4 weeks ($n = 17$).

A retrospective review of the medical charts of the patients was conducted to determine the gender, age, smoking history, body weight loss, performance status, clinical stage, histology, success of treatment delivery, incidence/severity of hematological toxicity and esophagitis, tumor responses, and survival parameters. The histological classification of the tumor was based on the criteria of the World Health Organization (11). Toxicity was graded according to the Common Terminology Criteria for Adverse Events v3.0. Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (12).

Statistical Methods

The demographic, clinical and histopathologic characteristics were compared between the genders. The χ^2 and Mann–Whitney tests were used to evaluate the differences in the categorical and continuous variables, respectively. Overall survival was measured from the start of chemotherapy to death from any cause. For progression-free survival (PFS), both the first evidence of disease progression and death from any cause were counted as an event. A patient who did not develop any event at the last follow-up was censored at that time. Survival curves were calculated according to the Kaplan–Meier method. Cox's proportional hazard models were used to adjust for potential confounding factors such as tumor stage and performance status (13). The significance of P value was set to be <0.05. All of the above-mentioned analyses were performed using the Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Demographics

Of the 204 patients, 44 (22%) were females and 160 (78%) were males (Table 1). There were no differences in age, body weight loss or performance status between the sexes, whereas never-smokers were more common among female patients (55% vs. 3%, $P < 0.001$). Adenocarcinoma accounted for the main histological type in both sexes, but was more common in female patients (73% vs. 55%, $P = 0.034$). No difference in the distribution of the clinical stage was noted between the sexes.

Treatment Delivery

The delivery of chemoradiotherapy was good in both sexes. Three to four cycles of chemotherapy were administered in 68% of the female patients and 69% of the male patients. A total radiation dose of 60 Gy was given to 89% of the female patients and 86% of the male patients.

Toxicities

Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients (Table 2). The frequency of febrile neutropenia was also the same between the sexes. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex.

Treatment after Recurrence

The use of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) was evaluated in

43 of the 44 female patients and 153 of the 160 male patients. Gefitinib was given to 7 female and 25 male patients, and erlotinib to 1 female and 1 male patient. Thus, in all, EGFR-TKIs were given to 8 (18.2%) female and 26 (16.3%) male patients.

Table 1. Patient characteristics

Characteristics	Female ($n = 44$)		Male ($n = 160$)		*P* value
	N	%	*N*	%	
Age					
Median (range)	57 (29–74)		58 (35–78)		0.28
Smoking history					
Never	24	55	5	3	<0.001
Former	5	11	77	48	
Current	15	34	78	49	
Body weight loss					
≤4.9%	36	82	126	79	0.66
≥5.0%	8	18	34	21	
Performance status					
0	12	27	51	32	0.62
1	32	73	107	67	
2	0		2	1	
Histology					
Adenocarcinoma	32	73	88	55	0.034
Non-adenocarcinoma	12	27	72	45	
Stage					
IIIA	17	39	69	43	0.53
IIIB	27	61	91	57	
Period					
1994–99	17	39	47	29	0.24
2000–05	27	61	113	71	

Table 2. Grade 3–4 toxicity

Toxicity	Grade	Female ($n = 44$)		Male ($n = 160$)		*P* value
		N	%	*N*	%	
Leukopenia	3	23	52	79	49	0.44
	4	9	21	33	21	
Neutropenia	3	13	30	49	31	0.19
	4	15	34	51	32	
Thrombocytopenia	3	1	2	5	3	0.97
	4	0		1	1	
Febrile neutropenia	3	9	21	37	23	0.59
	4	1	2	1	1	
Esophagitis	3	2	5	14	9	0.79

Response and Survival

There were 3 patients showing complete response (CR), 38 showing partial response (PR) and 2 showing stable disease (SD) among the 43 female patients evaluable for response, and 10 patients showing CR, 116 showing PR, 24 showing SD and 7 showing progressive disease among the 157 male patients evaluable for response. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$). Disease progression was noted in 36 of the 44 (82%) female patients and 131 of the 160 (82%) male patients. The median PFS did not differ significantly between the sexes: 9.2 months in the females and 9.7 months in the males ($P = 0.67$, Fig. 1). The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$, Fig. 2). Survival analyses in subgroups showed the

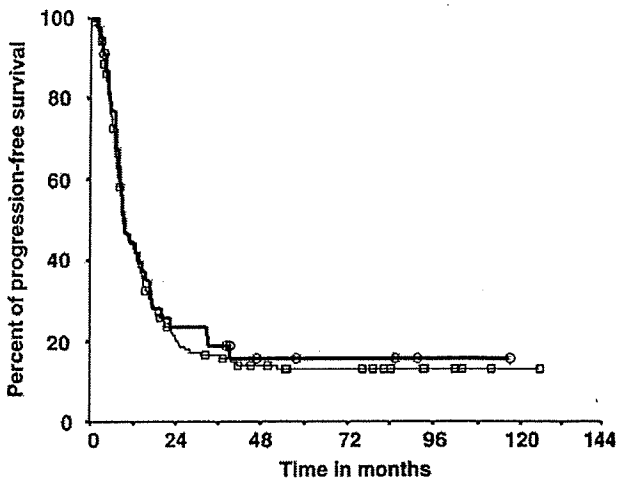

Figure 1. Progression-free survival by sex. Thick line, females; thin line, males.

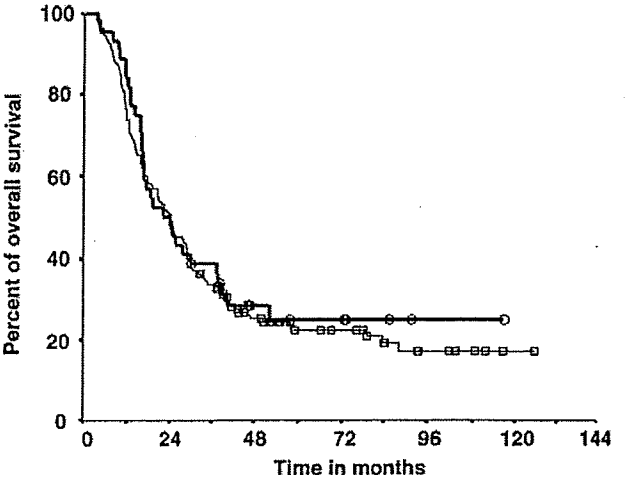

Figure 2. Overall survival by sex. Thick line, females; thin line, males.

Table 3. Factors associated with overall survival

Variables	Hazard ratio (95% confidence interval)	
	Univariate analyses	Multivariate analyses
Age	1.01 (0.99–1.03)	—
Sex		
Female	1	1
Male	1.10 (0.74–1.62)	1.16 (0.71–1.90)
Smoking habit		
No	1	1
Yes	1.00 (0.63–1.59)	0.75 (0.41–1.36)
Body weight loss		
≤4.9%	1	—
≥5.0%	1.19 (0.81–1.75)	—
Performance status		
0	1	1
1–2	1.59 (1.11–2.28)	1.44 (0.97–2.15)
Histology		
Adenocarcinoma	1	1
Non-adenocarcinoma	0.76 (0.53–1.10)	0.74 (0.51–1.08)
Stage		
IIIA	1	1
IIIB	0.96 (0.70–1.32)	0.79 (0.56–1.11)
Period		
1994–99	1	1
2000–05	0.62 (0.45–0.86)	0.65 (0.45–0.92)

absence of any gender differences either among patients with adenocarcinoma or among those with non-adenocarcinoma. Similarly, no gender differences were observed either among smokers or among never-smokers. Univariate Cox's proportional hazard analyses showed that the performance status and treatment period were significantly associated with the survival (Table 3). After adjustment for the smoking history and histological type, the gender had no impact on the overall survival (Table 3).

DISCUSSION

Although prospective cohort studies and a population-based study have reported better survival in women than in men with NSCLC, these results may be biased by potential confounding factors, because these studies included highly heterogeneous patients in terms of the stage, therapy, co-morbidities and other prognostic factors (2–4). Thus, whether there is any significant difference in survival between male and female patients receiving radiation-based treatment remained controversial, and this study failed to show any significant gender difference in the survival in NSCLC patients receiving concurrent chemoradiotherapy.

Several previous studies have suggested a better prognosis in female than in male NSCLC patients treated by surgery (2,14–18), whereas our results were inconsistent with this suggestion. This may be attributable to the difference in the distribution of the disease stage (pathological stages I, II and III) between these studies and our study, including pathological stages I, II and III. The magnitude of the gender difference in survival has been suggested to vary with the disease stage. Some studies have shown a diminishing gender difference as the disease stage advanced from stages I to III, with disappearance of the gender difference among patients with stage III disease (14,15), whereas others have shown relatively constant gender difference through all the disease stages (2,16,17). A study on the gender difference in the survival in surgically resected NSCLC patients showed a better overall survival in women than men, but no significant difference in the cancer-specific survival between the two sexes (18). These results suggest that the gender difference in survival in NSCLC patients undergoing curative surgery, especially patients with early-stage disease, can be explained by the mortality related to diseases other than lung cancer.

Among local or locally advanced NSCLC patients receiving radiotherapy-based treatment, the gender difference in survival has been controversial (5–9), but potential confounding factors in these studies prevent an accurate interpretation of the results. In these studies, as high as 30% of the patients had medically inoperable stage I–II disease and 3–22% of the patients had a performance status of 2. In addition, 36–100% of patients were treated by thoracic radiation alone, whereas the others also received some form of chemotherapy as part of the treatment. Neither the current study nor another previous study showed any gender difference in the survival (10). The patients in both of these studies were limited to stage III NSCLC patients with a performance status of 0–1 who were treated by concurrent chemoradiotherapy.

Several studies have been conducted on the gender differences in survival among patients with stage IIIB–IV disease treated by systemic chemotherapy (19–24). Of these, many showed a better survival in female patients than in male patients (19–22), but the causes of this gender difference in survival remain unknown. Our previous study also showed a better survival in female patients, which was explained partly by the large number of female patients (56% vs. 44%) receiving gefitinib, and the 4-fold longer duration of gefitinib treatment (144 vs. 35 days) in these patients (25). In contrast, only 18% of the female patients and 16% of the male patients received EGFR-TKIs in this study. Thus, treatment with EGFR-TKIs had little influence on the patient survival in this study.

Clear difference in the frequency of adenocarcinoma and smoking history between female and male patients has been reported repeatedly, and this study also showed that adenocarcinoma and never-smokers were more common among the female patients. Thus, it would be reasonable to think that differences in the tumor cell characteristics between the

female and male patients may be responsible for the difference in survival between the two sexes. However, survival analyses conducted separately in subgroups among patients with adenocarcinoma and those with non-adenocarcinoma, or among smokers and non-smokers have failed to reveal any gender differences in the survival among any subgroups. In addition, a multivariate analysis showed no difference in survival between the sexes after adjustment for the tumor histology and smoking history.

The threshold for drug toxicity may also differ between women and men. In general, chemotherapy-related toxicity is reported to be slightly more severe in women, and to the best of our knowledge, there are no reports on the gender difference in radiation-related toxicity. This study showed no difference in the severity of esophagitis or hematological toxicity between the two sexes. We did not examine pulmonary toxicity in this study, because our previous large retrospective study showed no difference in the incidence or grade of pulmonary toxicity between the sexes (26).

Among several limitations of this study, the most important is the small sample size that made it difficult to draw definitive conclusions. Indeed, small difference in survival between the sexes, if any, could not be detected in this small number of patients. It is difficult, however, to expand the study population without an increase in its heterogeneity. A population-based study with >20 000 patients, for example, included patients with all stages of lung cancer, and the therapies administered were not specified. Furthermore, the quality of data on diagnosis and treatment was not uniform (4). Thus, the results of that study may be biased, despite of the huge number of patients. We cannot overlook this problem especially when analyzing stage III NSCLC patients treated with radiation-based treatment, because the quality control of radiotherapy has not been fully developed in Japan, and therefore, indication, methods and outcomes of thoracic radiotherapy may vary among hospitals.

In conclusion, this study failed to reveal any significant differences in the treatment outcomes, including survival and treatment toxicity, between female and male patients with stage III NSCLC receiving concurrent chemoradiotherapy. These results are in sharp contrast to the reported better survival in female patients with localized disease treated by surgery or those with metastatic disease treated by systemic chemotherapy.

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Conflict of interest statement

None declared.

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