Table I. Patient characteristics.

	Patients with IBTR (n=505)	Patients without IBTR (n=1258)	P-value
Age	49.8±12.2	49.8±9.9	N.S.
Method of surgery			P=0.082
Quadrantectomy	129	211	
Wide excision	362	572	
Tumorectomy	8	3	
Other	0	2	
Unknown	6	470	
T stage[a]			P=0.017
T0	4	0	
T1	169	402	
T2	153	256	
T3	3	1	
Unknown	176	599	
N stage[a]			P=0.000
N0	193	570	
N1	121	159	
N2	26	15	
N3	0	1	
Unknown	165	513	
Stage[a]			P=0.000
Stage 0	5	0	
Stage 1	142	349	
Stage 2a	119	233	
Stage 2b	73	71	
Stage 3a	27	7	
Unknown	139	658	
Margin status			P=0.000
>5 mm	302	750	
≤5 mm	139	219	
Unknown	63	289	
Hormone receptor stastus			P=0.000
Positive	236	715	
Negative	184	289	
Unknown	85	254	
Radiation therapy			P=0.000
Yes	356	1146	
No	148	69	
Unknown	1	43	

IBTR, Ipsilateral Breast Tumor Recurrence. [a]General rules for clinical and pathological recording of breast cancer. 14th edition, The Japanese Breast Cancer Society.

KBCRTSG. The data format was developed by the steering committee of KBCRTSG and includes patient characteristics, including clinicopathological findings, method of BCT and outcome.

Table II. Details of IBTR.

	Patients with detailed information of IBTR (n=245)	
Location of IBTR		
TR/MM[a]	168	68.6%
Other than TR/MM	65	26.5%
Unknown	12	4.9%
Type of IBTR		
Nodular	209	85.3%
Diffuse	32	13.1%
Nodular/diffuse	3	1.2%
Method of salvage		
Partial mastectomy	119	48.6%
With RT	36	14.7%
Total mastectomy	102	41.6%
With RT	3	1.2%
Unknown surgery	6	2.4%
With RT	2	0.8%
No surgery	18	7.3%
With RT	2	0.8%
Re-IBTR		
No	193	78.8%
Yes	27	11.0%
Unknown	25	10.2%

[a]True recurrence/marginal miss: Recurrence within or adjacent to original tumor bed.

Eligibility criteria for this study were as follows: i) Japanese female, ii) received BCS alone or BCT, including RT, at participating hospitals of KBCRTSG, iii) has outcome data regarding both local and systemic control and iv) longer than 5-year follow-up for patients without IBTR.

Thus, 1813 cases without IBTR were excluded due to shorter follow-up than 5 years. Consequently, 505 cases of IBTR and 1258 cases of no IBTR were subjected to further analyses. Of note, 173 of the former and 70 of the latter had distant metastasis in their disease course. Patient characteristics are shown in Table I.

Statistical analyses. Univariate and multivariate Cox regression analyses were used to evaluate the impact of patient and treatment factors on the endpoint. Pearson's Chi-square test was used to evaluate the distribution of the patients' background. A p-value of <0.05 was regarded as significant.

Results

Details of IBTR were available for 245 of 505 patients with IBTR (Table II), the location of IBTR was within or adjacent to original tumor bed in 168 patients (68.6%), in another location in 65 patients (26.5%) and unknown in 12 patients (4.9%). The type of IBTR was nodular in 209

Table III. Univariate analyses.

	No. of available patients	RR	95% C.I.	P-value
Age	1748	1.011	1.003-1.020	P=0.006
Radiation therapy	1722	0.276	0.229-0.333	P=0.000
T stage	986	1.391	1.121-1.725	P=0.003
N stage	1085	1.808	1.503-2.174	P=0.000
Stage	1032	1.328	1.178-1.498	P=0.000
Margin status	1390	1.471	1.194-1.812	P=0.000
Hormone receptor status	1424	0.593	0.487-0.721	P=0.000
Method of surgery	1309			
Method (1) quadrantectomy		90.410[a]	0.000-5.95x10[17]	P=0.808
Method (2) wide excision		205.605[a]	0.000-1.35x10[18]	P=0.774
Method (3) lumpectomy		612.053[a]	0.000-4.04x10[18]	P=0.730

[a]Relative risk against method (4) 'other method'.

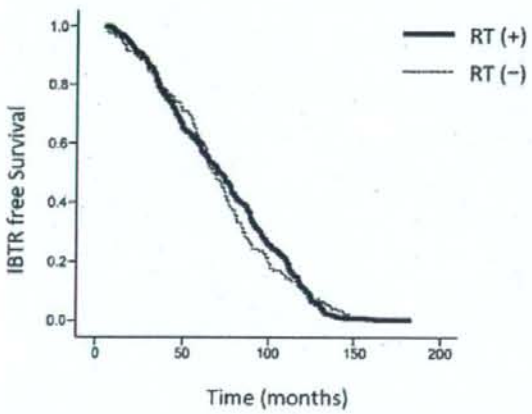

Figure 1. Kaplan-Meier estimate of ipsilateral breast tumor recurrence (IBTR)-free survival of the patients who eventually had IBTR. Note that the rate of IBTR is fairly consistent through 10 years.

patients (85.3%), diffuse/inflammatory in 32 patients (13.1%) and a combination of these in 3 patients (1.2%). IBTR was salvaged with partial mastectomy in 119 patients (48.6%), total mastectomy in 102 patients (41.6%), unknown surgery in 6 patients (2.4%) and no surgery in 18 patients (7.3%), of whom radiation therapy was used as a component of salvage therapy in 36 (14.7%), 3 (1.2%), 2 (0.8%) and 2 (0.8%). Second IBTR was observed in 27 patients (11.0%). Univariate analyses demonstrated that the administration of RT, resection margin status, hormone responsiveness, T stage, N stage and stage were significantly related to IBTR. Univariate analyses demonstrated that the administration of RT, resection margin status, hormone responsiveness, T stage, N stage and stage were significantly related to IBTR (Table III). The test for correlation among these variables demonstrated that several variables are dependent on each other (Table IV). Among them, stage was strongly correlated to T stage and N stage; therefore, RT, resection margin status, hormone responsive-ness, T stage and N stage were employed as variables for multivariate analysis using the Cox regression model. This demonstrated that RT, T stage and N stage were significantly correlated to IBTR. Among them, administration of RT had the largest impact on RT and decreased the risk of IBTR by 77.3% (Table V).

The IBTR-free survival curve was plotted for patients who eventually developed IBTR (Fig. 1). It revealed that the risk of IBTR is fairly constant over time both for patients who received RT and patients who did not.

Discussion

Several factors may influence the risk of local recurrence after BCT. Among them, administration of RT has been shown to have a large impact on local control, as shown in this study. According to a meta-analysis by EBCTCG, the effect of RT after BCS is highly consistent and reduces the risk of isolated IBTR by ~70% compared to those allocated to no RT (5). Other factors which are known to increase the risk of IBTR include young age, positive resection margin and existence of EIC.

There have been continuous efforts to identify a subgroup of patients for whom RT after BCS can be safely omitted. In the Joint Center for Radiation Therapy at Harvard Medical School, women considered to be at low risk for IBTR were prospectively observed without RT after BCS. The patients in this study had pT1N0 tumor, absence of both lympho-vascular invasion and extensive intraductal component and no cancer cells within 1 cm of resection margins. This study was terminated before it reached accrual goal because of an excessive number of IBTR. Of note, there were no eligibility limitations on patient age for this study and these patients did not receive any adjuvant chemo-endocrine therapy regardless of the status of hormone receptors (12). Considering that young age is a known risk factor for IBTR (13-19) and that systemic adjuvant therapy provides a benefit for local control (20,21), some patients in this study may not have been at low risk for IBTR. Previously, the CALGB C9343 trial demonstrated that it is a realistic choice for the treatment of

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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Original article

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

Naoko Sanuki-Fujimoto [a,*], Minako Sumi [a], Yoshinori Ito [a], Atsushi Imai [a], Yoshikazu Kagami [a], Ikuo Sekine [b], Hideo Kunitoh [b], Yuichiro Ohe [b], Tomohide Tamura [b], Hiroshi Ikeda [a]

[a] Department of Radiation Oncology, National Cancer Center Hospital, Japan
[b] Department of Thoracic Oncology and Internal Medicine, National Cancer Center Hospital, Japan

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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.

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,

* Corresponding author. Address: Department of Radiation Oncology, National Cancer Center Hospital, 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan.
E-mail address: naoS-tky@umin.ac.jp (N. Sanuki-Fujimoto).

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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

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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.

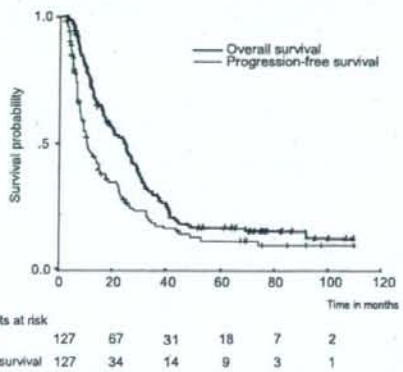

Fig. 1. Overall and progression-free survival curves of all the 127 patients. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

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 sys-

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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

temic 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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The Oncologist®

Local Control of Regional and Metastatic Lesions and Indication for Systemic Chemotherapy in Patients with Non-Small Cell Lung Cancer

IKUO SEKINE,[a] MINAKO SUMI,[b] NAGAHIRO SAIJO[c]

[a]Division of Internal Medicine and Thoracic Oncology, and
[b]Division of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan;
[c]Division of Internal Medicine, National Cancer Center Hospital East, Kashiwa, Japan

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ABSTRACT

Systemic chemotherapy is the mainstay of treatment in patients with advanced non-small cell lung cancer. Local control of regional and metastatic lesions may be needed before systemic therapy can be started in patients with pleural effusions or bone or brain metastases. The indication for systemic chemotherapy depends on the symptoms and performance status of the patient. In addition, a risk assessment considering complications such as hemodynamic and respiratory compromise by effusions, pathological bone fractures, and neurologic deterioration caused by brain metastases is critical in selecting which patients should receive first-line systemic chemotherapy before local therapy, although predictive factors for these complications have not yet been established. Chemotherapy has been considered to have only a limited role in the treatment of patients with pleural effusions and brain and bone metastases, but recently developed anticancer agents have shown substantial antitumor effects in these types of patients with a good general condition. *The Oncologist* 2008:13(suppl 1):21–27

INTRODUCTION

The majority of patients with non-small cell lung cancer (NSCLC) develop distant metastases either by the time of the initial diagnosis or during recurrence following surgery for the primary lesion. While systemic chemotherapy is the mainstay of treatment in patients with advanced NSCLC, local control of regional and metastatic lesions may be needed before systemic therapy can be used in patients with pleural effusions, bone metastases, or brain metastases. The general rule about whether local control should precede systemic chemotherapy varies according to the performance status (PS) of a patient and the responsiveness of the tumor to chemotherapy. If possible, systemic chemotherapy should be employed early in patients with malignant lymphoma and germ-cell tumors, as they are highly responsive and can be cured even at an advanced stage. It is unlikely that small-cell lung cancer can be cured, but because it responds well to chemotherapy, chemotherapeutic agents are frequently given prior to local therapy. In patients with advanced NSCLC, however, local therapy is often required before chemotherapy is administered because of the limited efficacy of chemotherapy in these patients.

PLEURAL EFFUSIONS

Malignant pleural effusions are a common clinical problem in patients with neoplastic disease, and may be the first presenting sign in as many as 10% of patients. Indeed, approximately 15% of lung cancer patients present with malignant pleural effusions at diagnosis [1]. In fact, lung cancer is the most common cause of malignant pleural effusions,

Correspondence: Ikuo Sekine, M.D., Ph.D., Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Telephone: 81-3-3542-2511; Fax: 81-3-3542-3815; e-mail: isekine@ncc.go.jp
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accounting for 17%–56% of cases [2]. Dyspnea is the most common symptom in patients with malignant effusions, occurring in more than half of cases, followed by cough and chest pain, although 5%–25% of patients have no respiratory complaints [3].

PS is significantly associated with survival in patients with pleural effusions [4]. Pleural effusions have been treated with the aim of palliation because NSCLC patients with pleural effusions are advanced stage by definition; massive effusions can cause hemodynamic and respiratory compromise, and the development of a symptomatic pleural effusion can drastically alter the quality of life and survival of patients [2]. Recently, however, as a result of the availability of ultrasound, computed tomography (CT), and positron emission tomography scans, NSCLC patients with small, asymptomatic pleural effusions can now be identified, and the treatment approach can be reconsidered in the setting of systemic disease control because relatively effective chemotherapy regimens have been developed.

It should be noted that pleural effusions can affect drug pharmacokinetics: methotrexate administered i.v. to patients with massive effusions is slowly released from third-space fluid, resulting in prolongation of the terminal half-life of the drug in the plasma, and potentially also increasing its toxicity [5, 6]. Similarly, levels of 5-fluorouracil decline rapidly in the plasma, but persist for longer in the effusion [7]. The pharmacokinetics of other drugs in patients with effusions are poorly studied, but drugs may accumulate in effusions and only slowly be redistributed throughout the body [8].

Patients with a small pleural effusion causing no symptoms can be treated with primary systemic chemotherapy, although there is a risk that the effusion will become symptomatic and require therapy. Patients with effusion-related dyspnea and those with a massive pleural effusion should be treated with a therapeutic thoracentesis; a large-volume thoracentesis allows rapid relief of symptoms in many patients. If systemic disease progression is a significant concern, an initial thoracentesis may create a window of opportunity in which to gain control over symptoms before starting chemotherapy. For patients whose effusions recur rapidly, more aggressive interventions may be required to achieve durable palliation, including chest tube drainage followed by chemical pleurodesis, and thoracoscopy with talc poudrage [8]. If patients gain durable palliation and are restored to a good PS by these treatments, then systemic chemotherapy is indicated. If not, their condition is suggestive of terminal-stage disease with a very short life expectancy.

Patients with NSCLC and pleural effusions are commonly included in chemotherapy clinical trials while they retain a good PS. Although the control of effusions by systemic chemotherapy has rarely been described, the efficacy of chemotherapy in treating effusions is considered to be comparable to the systemic response to chemotherapy. A retrospective study of 34 NSCLC patients with malignant pleural effusions treated with cisplatin, ifosfamide, and irinotecan showed that effusions disappeared for >4 weeks in 13 (38%) patients, while a partial response in measurable primary or metastatic lesions was obtained in 25 (66%) patients [9]. Active mutations of epidermal growth factor receptor (EGFR) have been detected in samples of pleural effusion fluid, and in patients with NSCLC they were associated with a clinical response to gefitinib, an EGFR tyrosine kinase inhibitor [10]. These results suggest that, in the near future, investigation of pleural effusion fluid could be important in selecting a chemotherapy regimen in patients with advanced NSCLC.

Brain Metastases

Lung cancer is the most common primary source of brain metastases, which develop in 10%–64% of lung cancer patients during the clinical course of the disease [11]. Even among newly diagnosed, asymptomatic patients with potentially operable NSCLC, routine brain scans identify brain metastases in 3%–10% of patients [12]. It is believed that the incidence of brain metastases is increasing as a result of an aging population, better control of extracerebral disease by more active systemic therapy, and better detection of small metastases following the development of imaging modalities such as magnetic resonance imaging (MRI).

Two thirds of cancer patients found to have brain metastases at autopsy had experienced neurologic symptoms resulting from the metastases, with only 10% of patients diagnosed by CT or MRI between 1973 and 1993 being asymptomatic [13]. Symptoms include headache, focal weakness, nausea, vomiting, and altered mental status. Seizures occur in about 20% of patients with brain metastases. When lung cancer patients are routinely screened, only 10% present to the physician with symptoms of brain metastases [12]. Thus, although the exact percentage is unknown, there are many patients with NSCLC who have brain metastases but no neurologic symptoms. The prognosis for patients with brain metastases is influenced largely by PS, age, and control of the primary and extracranial tumors. Whole brain radiotherapy (WBRT), with or without stereotactic irradiation, has been the treatment of choice for most patients with brain metastases, with a median survival time of 3–6 months after radiotherapy. This relatively short survival is related to progressive systemic disease rather than the brain metastases [11]. Therefore, systemic chemotherapy can be administered in many patients with brain metastases and is in fact important for their survival.

Chemotherapy has not been thought to have a major role in the treatment of patients with brain metastases because of a poor PS in many cases and the prevailing belief that the blood–brain barrier (BBB) may play a role in limiting delivery of chemotherapeutic agents to the central nervous system. However, the accumulation of contrast medium during CT or MRI assessments and the development of edema surrounding metastatic lesions suggest that tumor-induced vessels do not possess normal anatomical and physiological properties, and the BBB at the site of established brain metastases may be partly disrupted [14]. While one study demonstrated that the concentration of cisplatin in the brain metastases of patients who received the agent before surgery did not differ from that found in extracranial metastases [15], another study found that paclitaxel concentration in brain metastases was in the therapeutic range, while in brain tissue the concentration was below the limit of detection [16]. This observation is supported by objective response rates of brain metastases to systemic chemotherapy of 27%–50% in previously untreated patients with NSCLC, which are comparable to systemic response rates (Table 1) [17–23]. Gefitinib has also been shown to be effective against brain metastases arising from NSCLC; objective responses were obtained in 13 of 25 case reports of gefitinib use in such patients [24]. Thus, systemic chemotherapy is an important treatment option for NSCLC patients with brain metastases, as long as a good PS is maintained without neurologic symptoms.

The advantages of administering chemotherapy before radiotherapy can be summarized as follows: (a) it is useful to judge the tumor's response to chemotherapy; (b) radiotherapy decreases blood supply to the tumor and thus may hamper the ability of chemotherapeutic agents to reach the metastases; and (c) chemotherapy delivered before radiotherapy may be less toxic to the brain than chemotherapy after radiotherapy, because radiotherapy may open the BBB and allow the entry of potentially neurotoxic agents. Evidence for this is available for methotrexate treatment, and may also apply to other agents [25]. A randomized phase III trial of cisplatin plus vinorelbine followed by WBRT (arm A; $n = 86$) versus the same chemotherapy with early concurrent WBRT (arm B; $n = 85$) in NSCLC patients with brain metastases showed that the respective intracranial response rates evaluated after two cycles of chemotherapy were 27% and 33%, and that the overall response rates were 21% and 20%. The median survival time was 5.5 months in arm A and 4.8 months in arm B ($p = .83$). There was no difference between the arms in terms of hematologic and neurologic toxicities. These results suggest that chemotherapy is effective against brain metastases arising from NSCLC, and that the timing (early or delayed) of WBRT does not influence the survival of these patients [21].

Bone Metastases

Bone metastases are common in patients with lung cancer, with an incidence of 30%–55% at autopsy. These metastases are usually osteolytic, and are distributed mainly in

Table 1. Chemotherapy in previously untreated non-small cell lung cancer patients with brain metastases

Study	Chemotherapy regimen	*n* of patients	Response rate (%)		Median survival time (months)
			Intracranial	Systemic	
Minotti et al. (1998) [17]	CDDP + TNP	23	35	30	4.8
Crinò et al. (1999) [18]	CDDP + IFM + MMC	120	39	23	NA
	CDDP + GEM	123	41	37	NA
Franciosi et al. (1999) [19]	CDDP + ETP	43	30	75	7.4
Fujita et al. (2000) [20]	CDDP + IFM + CPT	30	50	62	12.6
Robinet et al. (2001) [21]	CDDP + VNR	86	27	35	5.5
Bernardo et al. (2002) [22]	CBDCA + VNR + GEM	20	45	45	7.6
Cortes et al. (2003) [23]	CDDP + PTX + VNR or GEM	25	38	50	4.9

Abbreviations: CBDCA, carboplatin; CDDP, cisplatin; CPT, irinotecan; ETP, etoposide; GEM, gemcitabine; IFM, ifosfamide; MMC, mitomycin-C; NA, not available; PTX, paclitaxel; TNP, teniposide; VNR, vinorelbine.

the spine, pelvis, ribs, and extremities. The most common symptom of bone metastases is pain, which is either diffuse or localized. It is characteristically described as dull and constant in presentation, worsening at night. The pain gradually increases in intensity, and can be exacerbated by certain movements or positions, such as standing, walking, or sitting [26]. However, up to 25% of patients with bone metastases are free of pain, and patients with multiple bone metastases typically report pain in only a few sites. The factors that convert a painless lesion to a painful one are unknown [27]. As bone destruction progresses, mechanical weakness and loss of structural integrity lead to pathological fracture; spinal instability, defined as mechanical instability in the spine related to extensive bone destruction [28]; cord compression, and hypercalcemia [26, 29]. The prognosis for patients with bone metastases varies among the different tumor types. The median survival time from diagnosis of bone metastases in patients with prostate cancer or breast cancer is measurable in years, whereas for lung cancer it is only 6–7 months [29]. The second most important prognostic factor in patients with bone metastases is PS; the median survival time for patients with a Karnofsky PS score of <50, 50–70, or 80–100 who received radiotherapy to the metastatic site was 2–3 months, 5 months, and 12 months, respectively [30, 31].

Bone destruction and its complications severely limit the activity and mobility of patients. For patients with a high risk for these complications, radiotherapy is the treatment of choice and orthopedic interventions may be necessary in some cases [26, 29].

Pathologic fractures occur in 8%–30% of all cancer patients, with the ribs, vertebrae, and long bones being the most frequent fracture sites [26, 29]. A long-bone fracture, especially when located at the proximal part of the femur, has a detrimental effect on the quality of life of patients with advanced cancer. Important factors in predicting an impending fracture of the long bones are pain that is exacerbated by movement and radiographic findings such as a predominantly osteolytic appearance, a large lesion, and axial cortical involvement [32, 33].

Spinal instability is the cause of back pain in 10% of patients with advanced cancer [26]. It can cause unbearable pain that is mechanical in origin, and frequently the patient is only comfortable when lying still [26]. Neither radiation therapy nor chemotherapy, even if successful in controlling the tumor, will alleviate the pain. As in the treatment of pathological fractures of the long bones, stabilization of the vertebral segments is required for pain relief [28]. However, major surgery is associated with significant morbidity and mortality, and good results can be obtained only in carefully selected patients. Percutaneous vertebroplasty provides rapid and effective relief from the pain associated with spinal instability.

Spinal cord compression occurs in 2%–5% of cancer patients [34]. The incidence varies with the type of cancer, and is 2.6% for NSCLC [35]. The cumulative incidence for all cancers decreases with age: it is 4.4% for patients aged 40–50 years, 3.9% for patients aged 50–60 years, 2.9% for patients aged 60–70 years, 1.7% for patients aged 70–80 years, and 0.5% for those aged >80 years [34]. About 60%–80% of spinal cord compressions occur in the thoracic region, 15%–30% in the lumbar region, and 10% in the cervical region. Multiple compression sites occur in approximately 7%–14% of cases [26, 34]. Early diagnosis and treatment are important for successful rehabilitation, but 48%–96% of patients present with motor weakness, bladder dysfunction, and inability to walk. In 83%–96% of patients, the first symptom is pain at the affected site, which may have been present from as little as 1 day to as long as 2 years, with a median duration of 8 weeks. It is generally exacerbated by coughing, sneezing, and straining, and typically increases in intensity over several weeks. Thus, the development of back pain in a cancer patient is a warning sign for possible spinal cord compression [26, 34].

Asymptomatic patients with bone metastases are potentially candidates for initial systemic chemotherapy, unless they show no risk factors for structural complications in radiographic assessments. These patients have been included in clinical trials of systemic chemotherapy; however, only limited information is available on the efficacy of chemotherapy for bone metastases, mainly because it is difficult to assess response to treatment in the bone, and bone metastases are defined as nontarget lesions in the Response Evaluation Criteria in Solid Tumors [36]. In patients with breast cancer, objective response rates of osteolytic lesions to standard chemotherapy regimens vary in the range of 20%–60% [37]. There are currently no reports on the objective response of bone metastases to chemotherapy in patients with NSCLC, but pain relief has been observed in 30%–61% of NSCLC patients receiving cisplatin-based chemotherapy, gemcitabine, or gefitinib [38-40].

Bisphosphonates, pyrophosphate analogues with a phosphorus–carbon–phosphorus (P–C–P)-containing central structure that promotes binding to the mineralized bone matrix, provide an additional treatment strategy for metastatic bone disease. Approximately 25%–40% of i.v. administered bisphosphonates are excreted by the kidney, and the remainder binds avidly to exposed bone mineral around resorbing osteoclasts, leading to inhibition of bone resorption and apoptosis of osteoclasts [26]. In addition to clinical use for hypercalcemia of malignancy, bisphos-

phonates are a routine treatment to prevent skeletal-related events (SREs) in patients with metastatic breast cancer and multiple myeloma. A recent meta-analysis evaluating randomized trials in these patients that lasted for 6 months or longer showed that bisphosphonates led to a significantly lower risk, versus placebo, for vertebral fractures (odds ratio [OR], 0.69; 95% confidence interval [CI], 0.57–0.84), nonvertebral fractures (OR, 0.65; CI, 0.64–0.99), radiotherapy (OR, 0.67; CI, 0.57–0.79), and hypercalcemia (OR, 0.54; CI, 0.36–0.81). In contrast, trials of <6 months' duration did not show any significant results for any skeletal morbidity outcome [41]. In patients with NSCLC, however, the role of bisphosphonates in the treatment of bone metastases has been less investigated. A recent phase III trial of zoledronic acid, a new generation bisphosphonate that has 100-1,000 times the potency of pamidronate in vitro, showed that 4 mg zoledronic acid led to a significantly lower annual incidence of SREs (1.74 per year versus 2.71 per year; $p = .012$) and longer median time to first SRE (7.8 months versus 5.1 months; $p = .009$) compared with placebo in 773 patients with lung cancer and other solid tumors [42, 43]. There are no criteria regarding the indication and duration of bisphosphonate therapy in patients with NSCLC. Evidence of bone destruction on plain radiographs, which is suggestive of receiving a benefit of bisphosphonates in patients with breast cancer [44], also may be an important factor in patients with NSCLC.

The presence or absence of bone pain should not be a factor in initiating bisphosphonates in patients with breast cancer [44], but no reports are available on this issue in patients with NSCLC. Because a relatively long duration of treatment (>6 months) is required for patients to get a benefit from bisphosphonates, patient prognosis is considered another factor to determine the indication of this type of agent [26].

Treatment Algorithm

Pleural effusions, brain metastases, bone metastases, and their associated morbidities give rise to a vexing clinical problem in patients with advanced NSCLC. Approaches to treating these patients are illustrated in Figure 1. The use of systemic chemotherapy depends on the symptoms and PS of the patients. In addition, a risk assessment looking at complications is critical in selecting which patients should receive first-line systemic chemotherapy, although factors predictive of these complications have not yet been established. Chemotherapy has previously been considered to have only a limited role in the treatment of patients with pleural effusions and brain and bone metastases, but recently developed anticancer agents have been shown to have substantial antitumor effects in patients with a good general condition.

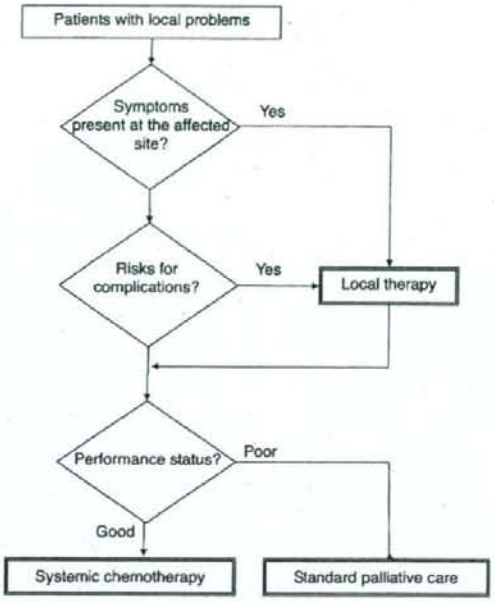

Figure 1. Treatment approaches for patients who have advanced non-small cell lung cancer with local problems.

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External-Beam Radiotherapy for Localized or Locally Advanced Prostate Cancer in Japan: A Multi-Institutional Outcome Analysis

Katsumasa Nakamura[1], Takashi Mizowaki[2], Hajime Imada[3], Katsuyuki Karasawa[4], Takashi Uno[5], Hiroshi Onishi[6], Keiji Nihei[7], Shigeru Sasaki[8], Masakazu Ogura[9] and Tetsuo Akimoto[10]

[1]Department of Radiology, School of Medicine, Fukuoka University, Fukuoka, [2]Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, [3]Department of Radiology, University of Occupational and Environmental Health, Kitakyushu, [4]Department of Radiation Oncology, Tokyo Metropolitan Komagome Hospital, Tokyo, [5]Department of Radiology, Graduate School of Medicine, Chiba University, Chiba, [6]Department of Radiology, School of Medicine, Yamanashi University, Yamanashi, [7]Radiation Oncology Division, National Cancer Center Hospital East, Kashiwa, Chiba, [8]Department of Radiology, Shinshu University, Matsumoto, [9]Department of Radiology, Tenri Hospital, Tenri, Nara and [10]Department of Radiology, Tokyo Women's Medical University, Tokyo, Japan

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Background: The outcomes of patients with localized or locally advanced prostate cancer treated with external-beam radiotherapy are not well known in Japan.
Methods: Thirty-four institutions combined data on 679 patients with localized or locally advanced prostate cancer treated with a total dose ≥60 Gy between 1995 and 2002.
Results: With a median follow-up of 46 months, the 5-year overall, clinical progression-free, and biochemical relapse-free survival rate were 93.0, 95.3 and 71.9% for all patients, respectively. The 5-year progression-free, and biochemical relapse-free survival rates according to the risk group were 100%, 90.8% in the low-risk group, 98.3%, 75.7% in the intermediate-risk group and 93.6%, 67.6% in the high-risk group, respectively. The multivariate analysis for biochemical relapse-free survival revealed that prostate-specific antigen (relative risk, 1.002; 95% CI, 1.001–1.003; $P = 0.0041$), Gleason score (relative risk, 1.166; 95% CI, 1.046–1.302; $P = 0.0055$), T classification (relative risk, 2.897; 95% CI, 1.999–4.230; $P = 0.0000$), pelvic irradiation (relative risk, 2.042; 95% CI, 1.328–3.273; $P = 0.0008$), and androgen ablation (relative risk, 0.321; 95% CI, 0.240–0.427; $P = 0.0000$) were significant prognostic factors. Only 1.1% of patients experienced late morbidity of Grade 3.
Conclusion: Radiotherapy for prostate cancer seemed to be effective, with little risk of normal tissue complications.

Key words: prostatic neoplasms – radiotherapy – treatment outcome

INTRODUCTION

Incidence rates, pathological features, clinical manifestation and the management of prostate cancer vary around the world. Although Asian people have the lowest incidence and mortality rates of prostate cancer in the world, these rates have risen rapidly in most Asian countries (1). In particular, the mortality rates for prostate cancer have been constantly and dramatically increasing in Japan with the increasingly aged population (2). Although screening for prostate cancer using prostate-specific antigen (PSA) has recently been introduced (3,4), most of the Japanese patients treated with external-beam radiotherapy (EBRT) still have high-risk prostate cancer (5,6). Radical radiotherapy is increasingly being accepted as an option for the curative treatment of prostate cancer (6), but the outcomes of patients with prostate cancer treated with EBRT are not well known in Japan and other Asian countries (7,8).

In the present multi-institutional retrospective study, we reviewed the clinical records of patients with localized or locally advanced prostate cancer treated with EBRT to analyse the clinical outcome of EBRT for prostate cancer in Japan.

For reprints and all correspondence: Katsumasa Nakamura, Department of Radiology, School of Medicine, Fukuoka University, Nanakuma 7-45-1, Jonan-ku, Fukuoka 814-0180, Japan. E-mail: nakam@fukuoka-u.ac.jp

PATIENTS AND METHODS

Of institutions belonging to the Japanese Radiation Oncology Study Group, 34 institutions with significant experience in radiotherapy collaborated in the present study (Appendix). We collected the clinical records of patients with localized or locally advanced prostate cancer who were irradiated with a total dose $\geq$60 Gy between 1995 and 2002. All patients had the following characteristics: a pretreatment PSA level, a biopsy Gleason score (GS), tumor classification (according to the International Union Against Cancer 2002 classification (9)), no clinical lymph node involvement, and a minimum follow-up interval of 2 years for living patients.

The total number of prostate cancer patients surveyed was 679. On the bases of PSA, GS and clinical T classification, risk groups were defined as low (T1–T2, GS $\leq$ 6 and PSA $\leq$ 10 ng/ml), intermediate (T1–T2, GS $\leq$ 7 and 10 $<$ PSA $\leq$ 20 ng/ml or T1–T2, GS = 7 and PSA $\leq$ 10 ng/ml) and high (T3–T4, GS $>$ 7, or PSA $>$ 20 ng/ml) (10). The patients' characteristics are shown in Table 1. More than 45% of the patients had T3 or T4 tumors. The median pretreatment PSA level was 17.7 ng/ml (range, 1.5–1250 ng/ml). Most of the patients (86.9%) belonged to the intermediate- or the high-risk group.

The treatment characteristics are shown in Table 2. Over 80% of patients received a combination of EBRT and hormonal therapy. Neoadjuvant hormonal therapy was performed in 76.7% of patients, while adjuvant hormonal therapy was used in 34.8%. The median durations of hormonal therapy before and after radiotherapy were 6 months (range, 1–68 months) and 38 months (1–109 months), respectively.

Megavoltage photon equipment was used to deliver radiation. Patients were treated with a variety of radiotherapy techniques (Table 2). The treatment plan included a moving field in 62.7% of patients. More than 80% of patients were treated using a conformal technique. Intensity-modulated radiation therapy (IMRT) was performed in only 2.4% of patients. Fraction sizes of 1.5, 1.8, 2.0, 2.4 and 3.0 Gy to the prostate were used in 1 (0.1%), 10 (1.5%), 643 (94.7%), 4(0.6%) and 21 patients (3.1%), respectively. The median total prescribed dose was 70.0 Gy (range, 60.0–78.0 Gy).

In most patients with PSA failure, the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition (11) was used: three consecutive rises in PSA level, backdating the time of failure to the midpoint between the last non-rising and the first rising PSA measurements. Also included as failure criteria were administration of hormonal therapy before three PSA rises, clinical failure as the first event, or a rise above a certain level of PSA. The median PSA level at the administration of salvage hormonal therapy was 3.2 ng/ml (0.024–341.3 ng/ml). Patients were categorized as having clinical failure if they developed local, regional or distant failure. The median follow-up was 46 months (range, 3–109 months) for all patients.

Table 1. Patients and disease characteristics

No. patients	679
Age	
Median	73 years
Range	49–88 years
Tumor classification/2002 UICC	
T1	110 (16.2%)
T2	256 (37.7%)
T3	300 (44.2%)
T4	13 (1.9%)
Pretreatment PSA level (ng/ml)	
$\leq$ 10.0	187 (27.5%)
10.1–20.0	178 (26.2%)
$>$ 20.0	314 (46.3%)
Biopsy Gleason score	
$\leq$ 6	268 (39.5%)
= 7	231 (34.0%)
8–10	180 (26.5%)
Risk classification	
Low	89 (13.1%)
Intermediate	140 (20.6%)
High	450 (66.3%)

PSA, prostate-specific antigen; UICC, International Union Against Cancer.

The overall survival rate and the progression-free survival rate were calculated from the first day of radiotherapy using the Kaplan–Meier method. Log-rank statistics were used to identify significant prognostic factors for survival. Cox's proportional hazard model was used in multivariate analysis. The Common Terminology Criteria for Adverse Events version 3.0 were used to assess the late morbidity.

RESULTS

Patterns of failure are shown in Table 3. PSA failure was seen in 160 patients (23.6%). Clinically, there were four local, four regional, three regional and distant and 17 distant failures after completion of radiotherapy. In patients in the low-risk group, there was no clinical failure. Only seven patients in the high-risk group died of prostate cancer, 31 died of intercurrent diseases and two died of unknown causes.

The 5-year overall, clinical progression-free and biochemical relapse-free survival rates were 93.0, 95.3 and 71.9% for all patients, respectively. The 5-year clinical progression-free, and biochemical relapse-free survival rates according to the risk group were 100%, 90.8% in the low-risk group, 98.3%, 75.7% in the intermediate-risk group and 93.6%, 67.6% in the high-risk group, respectively (Figs 1 and 2). Table 4 presents the results of multivariate analysis for