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

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

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

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Conflict of interest statement

None declared.

References

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

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Original Article

Zoledronic acid delays disease progression of bone metastases from hepatocellular carcinoma

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Aim: We conducted a retrospective cohort study to investigate the efficacy of combination therapy with radiotherapy (RT) and zoledronic acid for bone metastases from hepatocellular carcinoma (HCC). Additionally, we investigated the efficacy of zoledronic acid for non-irradiated bone metastases.

Methods: This study consisted of 31 patients who had received RT for bone metastases. Twelve of these patients with 23 sites of bone metastases were also treated with zoledronic acid (Z group). In the Z group, 14 sites received RT and nine sites did not. Nineteen patients with 38 sites of bone metastases were not treated with zoledronic acid (non-Z group). In the non-Z group, 22 sites received RT and 16 did not. We compared survival, pain response, time to pain progression, radiographic response, time to radiographic progression, and safety between groups.

Results: While pain response rates were similar between the two groups, time to pain progression rates of irradiated and non-irradiated bone metastases was significantly lower in the Z (0% and 20% at 6 months, respectively) than in the non-Z group (34% and 66% at 6 months, respectively) ($P = 0.045$ and $P = 0.005$). Further, while radiographic response rates were similar between the two groups, time to radiographic progression rate of non-irradiated bone metastases was significantly lower in the Z (29% at 3 months) than in the non-Z group (91% at 3 months) ($P = 0.009$). No significant side-effects were documented.

Conclusion: Zoledronic acid delayed the pain progression of both irradiated and non-irradiated bone metastases and the radiographic progression of non-irradiated bone metastases from HCC.

Key words: bone metastases, hepatocellular carcinoma, radiotherapy, zoledronic acid

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) remains one of the most common cancers and causes of cancer death worldwide.[1,2] The development of diagnostic techniques and advances in therapeutic modalities has improved the control of HCC and the prognosis of HCC patients.[3–5] As a result, the incidence of diagnosed extrahepatic metastases from HCC has gradually increased. It has been reported that bone is the second- or third-most frequent metastatic lesion from HCC and that 5.2–10.2% of HCC patients develop bone metastases.[6–8] Bone metastases cause intractable bone pain, resulting in a marked deterioration in quality of life.

Although radiotherapy (RT) provides effective pain relief for bone metastases from HCC,[9–11] the persistence of this pain relief remains unclear. In addition, the effect of RT in inducing the radiographic shrinkage of bone metastases and the persistence of this shrinkage is also unclear. Thus, the use of RT alone for these metastases may not be sufficient, and combination therapy with other modalities may be warranted.

Recently, zoledronic acid (Zometa; Novartis Pharma, Basel, Switzerland/Novartis Pharmaceuticals, East Hanover, NJ, USA), a highly potent nitrogen-containing

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bisphosphonate, has been reported to show efficacy against bone metastases from several solid tumors such as breast carcinoma, renal cell carcinoma and lung cancer.[12–14] Although the use of zoledronic acid in the treatment of bone metastases from HCC has also been reported,[15] bone metastases in this study were treated with several concomitant therapeutic modalities, namely sorafenib and chemotherapy, and the effectiveness of zoledronic acid for bone metastases from HCC thus remains unclear.

Here, we conducted a retrospective cohort study of RT with or without zoledronic acid for bone metastases from HCC. We investigated the additional effect of zoledronic acid for irradiated bone metastases from HCC. Further, because approximately half of the patients had non-irradiated bone metastases without pain or risk of spinal cord compression, we also investigated the effect of zoledronic acid alone for non-irradiated bone metastases. Measurement variables included pain response, radiographic response, time to pain progression, time to radiographic progression and safety.

METHODS

Patients and eligibility

THE STUDY WAS conducted under a retrospective cohort design to elucidate the efficacy of zoledronic acid for bone metastases from HCC. From January 2008, HCC patients with bone metastases from HCC were treated with zoledronic acid in our institution.

Enrollment criteria were age more than 18 years, Child–Pugh grade A or B, with bone metastases from HCC and at least one site of bone metastases were treated with RT. Concomitant therapies for intrahepatic HCC (e.g. transcatheter arterial chemoembolization, hepatic arterial infusion chemotherapy) were allowed. Exclusion criteria were previous bisphosphonate therapy, previous RT for bone metastases and concomitant percutaneous radiofrequency ablation or cementoplasty for bone metastasis.

For patients treated with zoledronic acid, serum creatinine level of 1.5 mg/dL or more, calculated creatinine clearance (Cr Cl) of 30 mL/min or less, corrected serum calcium level of 8 mg/dL or less and risk factors for osteonecrosis of the jaw (e.g. uncontrolled gingivitis and dental caries) were defined as exclusion criteria. In addition, for patients treated with zoledronic acid, concomitant systemic chemotherapy was defined as an exclusion criteria so that the efficacy of zoledronic acid avoided becoming inarticulate.

This study consisted of consecutive 31 HCC patients with bone metastases. From June 2008 to December 2009, 12 consecutive patients treated with RT and zoledronic acid were defined as the Z group. From May 2002 to June 2007, 19 consecutive patients treated with RT were defined as the non-Z group.

All patients of the Z group were asked to provide a written informed consent to this study, which was approved by the Institutional Review Board of Hiroshima University.

Diagnosis of HCC

Primary HCC was diagnosed by pathological examination or typical radiological findings (hypervascular tumor, diameter >2 cm) and tumor marker (α-fetoprotein [AFP] ≥400 ng/mL). Bone metastases were diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI). Other primary malignancies (e.g. gastric cancer, lung cancer, prostate cancer, renal cell carcinoma, breast cancer) were excluded by one or a combination of various imaging modalities, endoscopic examinations, serological tumor markers or pathological examinations.

Treatment protocol

Patients of the Z group received zoledronic acid by i.v. infusion for 15 min at a dose of 3–4 mg depending on creatinine clearance, namely more than 60 mL/min, 4 mg; 50–60 mL/min, 3.5 mg; 40–49 mL/min, 3.3 mg; and 30–39 mL/min, 3 mg. Administration was repeated every 4 weeks during survival period. Doses of 600 mg of calcium and 400 IU of vitamin D were administrated as daily supplements. All patients received RT for at least one site of bone metastasis. In the Z group, administration of zoledronic acid and RT commenced simultaneously. RT was performed for bone metastases with pain or the risk of spinal cord compression. A 3-D treatment planning system (Pinnacle 3; ADAC, Madison, WI, USA) was used for radiotherapy planning. Two or more beams were assigned according to the site and extension of the bone metastasis. The standard dose was 30 Gy given in 10 fractions. Total and fractionation dose were modified in consideration of the site and size of the lesion and the patient's condition. In case of spinal canal invasion, 39 or 45 Gy was prescribed.

After commencement of RT with or without zoledronic acid, analgesic was not increased unless pain score turned worse to evaluate the effects of RT with or without zoledronic acid for pain relief.

Evaluation

Pain response

Pain response to therapy was defined using a visual analog scale (VAS) and analgesic score.[10,16,17] The analgesic score was divided into phase 1 (non-opioid analgesics: paracetamol and non-steroidal anti-inflammatory drugs), phase 2 (non-opioid analgesic combinations with weak opioids), phase 3 (strong opioids, such as morphine) and phase 4 (non-oral administration of opioids). A change from phase 1 or 2 to phase 3 or 4 was noted as an analgesic increase. If the patient stopped using phase 3 or 4 analgesics, this was noted as an analgesic decrease. Complete pain relief was defined as a decrease in the initial pain score to zero on the pain scale without concomitant analgesic increase; partial pain relief as a decrease in the initial pain score by at least 2 points without analgesic increase, or an analgesic decrease without an increase in pain; progressive pain as an increase in pain score without analgesic increase, or an analgesic increase irrespective of pain score; and stable pain as meeting neither partial nor progressive pain criteria. Pain response was assessed every month, and the best response of the irradiated bone metastases was recorded, as was time to pain progression of irradiated and non-irradiated bone metastases. Because the pain score of most non-irradiated bone metastases at the initiation of therapy was zero, the pain response of these metastases could not be assessed.

Radiographic response

Measurable bone metastases were assessed by radiographic measurement. In accordance with the criteria of the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1,[18] lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components of more than 10 mm were considered as measurable bone metastases.

Radiographic response of bone metastases to therapy was assessed with contrast-enhanced CT or MRI at 2 months after the commencement of therapy and every 3 months thereafter. A complete response (CR) was defined as the disappearance of all existing bone metastases and no appearance of any new metastases. A partial response (PR) was defined as a decrease of at least 30% in the sum of the longest diameters of bone metastases and no appearance of any new bone metastases. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the longest diameters of bone metastases or the appearance of new metastases. Stable disease (SD) was defined as meeting neither the PR nor PD criteria.

Safety

Adverse reactions were assessed weekly during treatment using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (ver. 3.0).

Statistical analysis

Differences between groups were examined for statistical significance using the Mann–Whitney *U*-test, logistic regression test and χ^2-test where appropriate. Cumulative survival rate, time to pain progression and time to radiographic progression were calculated from the initial date of therapy for bone metastases from HCC and assessed by the Kaplan–Meier life-table method, with differences evaluated by the log-rank test. Statistical significance was defined as a *P*-value of less than 0.05. All analyses were performed using the SPSS program (ver. 18, SPSS, Chicago, IL, USA).

RESULTS

Patients

BASELINE CHARACTERISTICS OF patients of the two groups are shown in Table 1. In the Z group, five patients were administrated zoledronic acid 2–3 times, four were administrated 4–6 times and three were administrated 7–10 times. Patients of the Z group were older ($P = 0.02$), but there were no differences between the groups with regard to sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS),[19] etiology, Child–Pugh grade, AFP, des-γ-carboxy prothrombin (DCP), VAS score, analgesic score, number of bone metastases, number of irradiated bone metastases, radiation dose for one site of bone metastasis, concomitant therapy for intrahepatic HCC, concomitant systemic chemotherapy or duration of observation period.

In the Z group, 14 bone metastases received RT and nine did not. In the non-Z group, 22 bone metastases received RT and 16 did not. In the Z group, three of 14 (21%) irradiated and three of nine non-irradiated metastases (33%) were vertebral. In the non-Z group, nine of 22 (41%) irradiated and seven of 16 (44%) non-irradiated metastases were vertebral. For irradiated bone metastases, non-irradiated bone metastases and overall bone metastases, proportions of vertebral and

Table 1 Clinical profile of patients with bone metastases from hepatocellular carcinoma treated with or without zoledronic acid

	Z group	Non-Z group	*P*-value
Number of patients	12	19	
Age (years)†	68 (52–87)	58 (40–76)	0.02
Sex (male/female)	12/0	16/3	0.27
PS (1/2)	9/3	17/2	0.35
Etiology (HBV/HCV/others)	0/9/3	6/11/2	0.08
Child–Pugh grade (A/B)	9/3	18/1	0.27
AFP (ng/mL)†	710 (5–194 700)	5200 (13–24 1030)	0.21
DCP (mAU/mL)†	1776 (12–38 969)	200 (15–335 390)	0.70
VAS score†	4.5 (1–10)	4.0 (1–10)	0.74
Analgesic score (phase 1/2/3/4)	6/1/5/0	8/1/10/0	0.82
Number of bone metastases per patient (1/2,3/4,5)	6/4/2	11/4/4	0.75
Total number of bone metastases	23	38	
Number of irradiated bone metastases per patient (1/2,3)	11/1	16/3	1.0
Total number of irradiated bone metastases	14	22	
Radiation dose for one site of bone metastasis (Gy)†	30 (25–39)	39 (25–45)	0.15
Concomitant therapy for intrahepatic HCC (TACE/HAIC/not performed)	5/4/3	6/6/7	0.76
Concomitant systemic chemotherapy (performed/not performed)	0/12	5/14	0.13
Number of administrations of zoledronic acid (2–3/4–6/7–10 times)	5/4/3	–	
Duration of observation period (months)†	3.8 (1.2–10.0)	4.2 (2.4–12.5)	0.47

†Data are median values (range).
AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PS, Eastern Cooperative Oncology Group performance status; TACE, transcatheter arterial chemoembolization.

non-vertebral metastases did not statistically differ between the two groups as shown in Table 2.

Among irradiated bone metastases, 13 of 14 bone metastases in the Z group and 18 of 22 in the non-Z group were measurable. The median value of the maximum diameters of the tumors were 36 mm (range 21–53 mm) in the Z group and 32 mm (range 12–90 mm) in the non-Z group, respectively. Among non-irradiated bone metastases, seven of nine metastases in the Z group and 12 of 16 in the non-Z group were measurable. The median value of the maximum diameters of the tumors were 15 mm (range 11–22 mm) in the Z group and 13 mm (range 10–18 mm) in the non-Z group, respectively. There

Table 2 Sites of bone metastases from hepatocellular carcinoma treated with or without zoledronic acid

	Z group (12 patients, 23 bone metastases)			Non-Z group (19 patients, 38 bone metastases)			*P*-value
	Irradiated bone metastases	Non-irradiated bone metastases	Total	Irradiated bone metastases	Non-irradiated bone metastases	Total	
Skull	2	0	2	2	1	3	
Vertebra	3	3	6	9	7	16	
Rib/sternum/scapula	6	4	10	6	4	10	
Pelvis	3	1	4	2	4	6	
Long bone	0	1	1	3	0	3	
Vertebrae	3 (21%)			9 (41%)			0.29
Others	11 (79%)			13 (59%)			
Vertebrae		3 (33%)			7 (44%)		0.69
Others		6 (67%)			9 (56%)		
Vertebrae			6 (26%)			16 (42%)	0.28
Others			17 (74%)			22 (58%)	

Table 3 Size of bone metastases from hepatocellular carcinoma treated with or without zoledronic acid

	Number of non-measurable lesions	Number of measurable lesions	Size of measurable lesions (mm)†	*P*-value
Irradiated bone metastases				
Z group	1	13	36 (21–53)	
Non-Z group	4	18	32 (12–90)	0.75
Non irradiated bone metastases				
Z group	2	7	15 (11–22)	
Non-Z group	4	12	13 (10–18)	0.20

†Data are median values (range).

were no statistical differences between the two groups ($P = 0.75$ and $P = 0.20$) as shown in Table 3.

Pain response of bone metastases from HCC

Irradiated bone metastases

With regard to best pain response of irradiated bone metastases, complete pain relief, partial pain relief, stable pain and progressive pain were observed in six (43%), eight (57%), zero (0%) and zero (0%) of patients of the Z group, and in six (27%), 15 (68%), one (5%) and zero (0%) of patients of the non-Z group, respectively (Table 4). The pain response rates of the two groups were thus similar.

Time to pain progression of bone metastases from HCC

Irradiated bone metastases

In the Z group, pain progression of irradiated bone metastases was not recorded. Cumulative pain progression rates of irradiated bone metastases for patients of the non-Z group at 3 and 6 months were 19% and 34%, respectively. Cumulative pain progression rates was significantly lower in the Z group than in the non-Z group ($P = 0.045$, Fig. 1a).

Non-irradiated bone metastases

Cumulative pain progression rates of non-irradiated bone metastases for patients of the Z and non-Z groups at 3 and 6 months were 0% and 20%, and 58% and 66%, respectively, and thus significantly lower in patients of the Z group ($P = 0.005$, Fig. 1b).

Radiographic response of bone metastases from HCC

Irradiated bone metastases

With regard to best radiographic response of irradiated bone metastases, PR, SD and PD were observed in six (46%), seven (54%) and zero (0%) patients of the Z group, and in seven (39%), nine (50%) and two (11%) patients of the non-Z group, respectively (Table 5). The radiographic response rates of the two groups were thus similar.

Non-irradiated bone metastases

Among non-irradiated bone metastases, seven of nine metastases in the Z group and 12 of 16 in the non-Z group were measurable. With regard to best radiographic response of non-irradiated bone metastases, SD and PD were observed in five (71%) and two (29%) metastases in patients of the Z group, and in zero (0%) and 12 (100%) in the non-Z group, respectively. There was a statistically significant difference in disease control (CR, PR and SD) rates of non-irradiated bone metastases between the two groups (71% vs 0%, $P = 0.002$, Table 5).

Table 4 Pain response of irradiated bone metastases from hepatocellular carcinoma treated with and without zoledronic acid

	Number of bone metastases	Complete pain relief	Partial pain relief	Stable pain	Progressive pain	Response rate†	*P*-value
Irradiated bone metastases							
Z group	14	6 (43%)	8 (57%)	0	0	100%	1.0
Non-Z group	22	6 (27%)	15 (68%)	1 (5%)	0	95%	

†Response rate = complete pain relief + partial pain relief/complete pain relief + partial pain relief + stable pain + progressive pain.

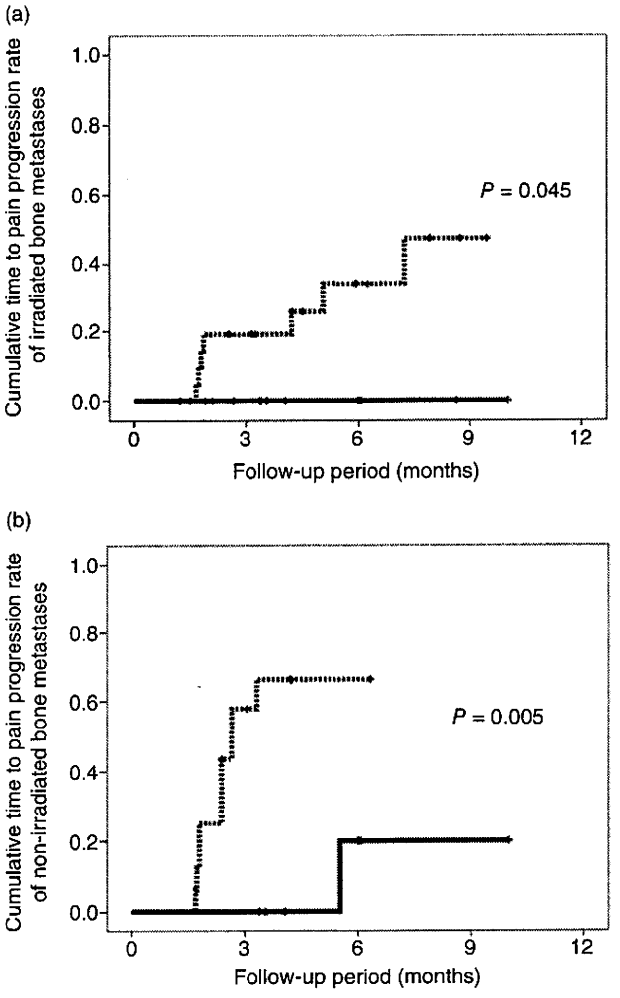

Figure 1 (a) Cumulative time to pain progression rate of irradiated bone metastases from hepatocellular carcinoma (HCC) (log-rank test). (——) Z group; (——) non-Z group. (b) Cumulative time to pain progression rate of non-irradiated bone metastases from HCC (log-rank test). (——) Z group; (——) non-Z group.

Time to radiographic progression of bone metastases from HCC

Irradiated bone metastases

In the Z group, radiographic progression of irradiated bone metastases was not recorded. Cumulative radiographic progression rates of irradiated bone metastases for patients of the non-Z group at 3 and 6 months were 29% and 43%, respectively. Cumulative radiographic progression rates of irradiated bone metastases in the two groups did not differ ($P = 0.11$, Fig. 2a).

Table 5 Radiographic response of irradiated and non-irradiated "measurable" bone metastases from hepatocellular carcinoma

	Number of measurable bone metastases	CR	PR	SD	PD	Response rate†	*P*-value	Disease control rate‡	*P*-value
Irradiated bone metastases									
Z group	13	0	6 (46%)	7 (54%)	0	46%	0.73	100%	0.50
Non-Z group	18	0	7 (39%)	9 (50%)	2 (11%)	39%		89%	
Non-irradiated bone metastases									
Z group	7	0	0	5 (71%)	2 (29%)	0%	1.0	71%	0.002
Non-Z group	12	0	0	0	12 (100%)	0%		0%	

†Response rate = CR + PR/CR + PR + SD + PD.
‡Disease control rate = CR + PR + SD/CR + PR + SD + PD.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

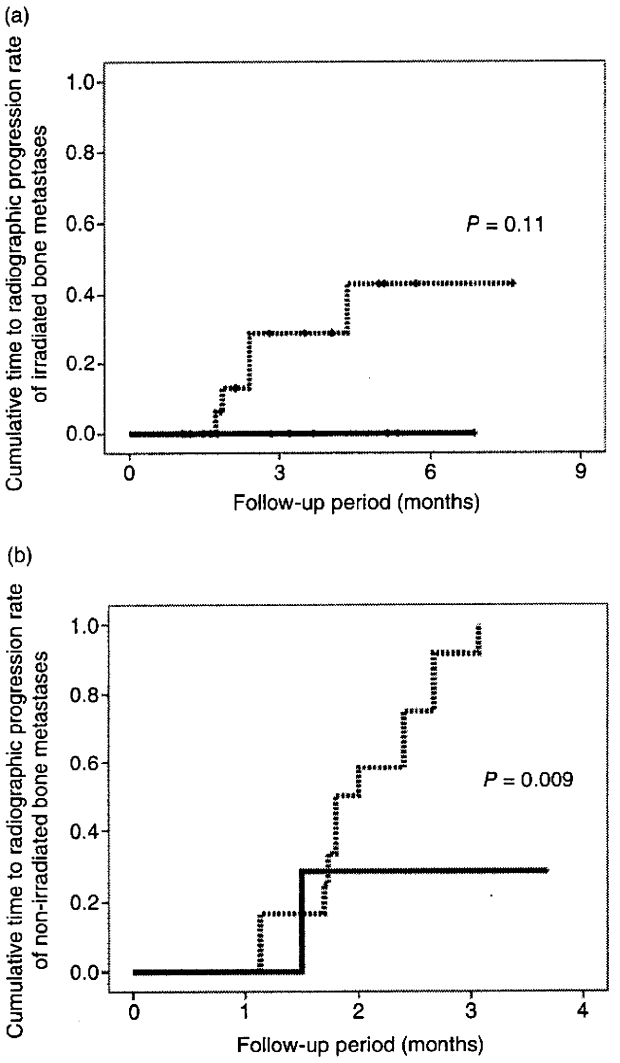

Figure 2 (a) Cumulative time to radiographic progression rate of measurable irradiated bone metastases from hepatocellular carcinoma (HCC) (log-rank test). (——) Z group; (– – –) non-Z group. (b) Cumulative time to radiographic progression rate of measurable non-irradiated bone metastases from HCC (log-rank test). (——) Z group; (– – –) non-Z group.

Non-irradiated bone metastases

Cumulative radiographic progression rates of non-irradiated bone metastases for patients in the Z and non-Z groups at 3 months were 29% and 91%, respectively, and thus significantly lower in the Z group ($P = 0.009$, Fig. 2b).

Performance status

No patient in the Z group and seven patients in the non-Z group worsened of PS due to bone metastases. Cumulative PS worsening rate in the non-Z group at 3 and 6 months were 23% and 40%, respectively. Cumulative PS worsening rates was significantly lower in the Z group than in the non-Z group ($P = 0.040$).

Survival

At the end of the observation period, four patients in the Z group were still alive and eight had died, whereas all 19 patients in the non-Z group had died. No patient in the Z group died of bone metastasis-related disease, whereas one patient in the non-Z group died of bone metastases-related disease, namely respiratory failure due to spinal compression by bone metastases.

Median survival time (MST) of patients of the Z and non-Z groups was 6.0 months (95% confidence interval [CI], 0.0–12.7 months) and 4.2 months (95% CI, 1.2–7.2 months), respectively, while cumulative survival rates at 3 months were 74% and 44%, and at 6 months were 79% and 37%, respectively. There was no statistically significant difference in survival rates between the two groups ($P = 0.72$).

Safety

In the Z group, no renal adverse reactions, osteonecrosis of the jaw or hypocalcaemia were observed during the treatment, and no patient required discontinuation of zoledronic acid due to adverse reactions.

DISCUSSION

IN THIS STUDY, we evaluated the efficacy of zoledronic acid in the treatment of bone metastases from HCC by comparing the clinical course of patients with bone metastases treated with or without zoledronic acid. Results showed that this drug delayed pain progression in both irradiated and non-irradiated bone metastases and delayed radiographic progression of non-irradiated bone metastases from HCC.

Zoledronic acid, a new-generation nitrogen-containing bisphosphonate, inhibits bone resorption by preventing prenylation of GTPases, such as Ras, Rac and Rho, which play key roles in regulating osteoclast function and events in bone resorption, and ultimately induces cell death in osteoclasts.[20,21] In addition, because prenylation is required by all cells, zoledronic acid inhibits the proliferation of and induces apoptosis in human cancer cells.[22] Although several studies have shown the clinical effects of zoledronic acid against the pain and tumor burden of bone metastases from several malignancies,[12–14] the effect of zoledronic acid for bone metastases from HCC has remained unclear.

Bone metastases from HCC cause intractable bone pain, bone fracture, spinal cord compression and hypercalcemia, all of which result in a deterioration in quality of life. RT has been widely used for the treatment of these metastases, including approximately 60% of those in the present patients. Although RT has been reported to improve pain in painful bone metastases from HCC in 72.7–99.5% of metastases,[9–11] the persistence of this pain relief has been unclear. It has been reported bone metastases from various solid tumors treated with RT at 24 Gy showed pain progression after initial pain relief in 47%.[17] In the present study, while the pain relief rates of irradiated bone metastases of both groups were similar, the pain progression rate of irradiated bone metastases was significantly lower in the Z than in the non-Z group ($P = 0.045$).

Bone metastases from HCC frequently occur as multiple metastases.[6,7] Because RT for multiple lesions elevates the risk of various adverse effects, such as bone marrow suppression, gastrointestinal ulcers and dermatitis, RT in these patients is generally initiated in those lesions causing pain, or with the possibility of causing spinal cord compression.[10] In the present study, approximately half of the bone metastases were not irradiated. Interestingly, the pain progression rate of non-irradiated bone metastases was significantly lower in the Z group than in the non-Z group ($P = 0.005$).

Our results demonstrated the efficacy of zoledronic acid in providing the persistence of pain relief of irradiated bone metastases. In addition, we showed that pain progression of non-irradiated bone metastases was restricted by zoledronic acid alone. However, nearly all painful bone metastases in the present study received RT, and most non-irradiated metastases showed no pain. The efficacy of zoledronic acid alone for pain relief is still therefore unclear, and further studies are needed.

We also investigated the efficacy of zoledronic acid with regard to the radiographic response of bone metastases. Previous studies have reported a synergistic effect of zoledronic acid combined with RT in a mouse model,[23] and a significantly higher response rate of bone metastases from renal cell carcinoma in patients treated with RT plus zoledronic acid than in those treated with RT alone (60% vs 8%, $P = 0.019$).[24] In the present study, in contrast, the response rates of irradiated bone metastases of the Z and non-Z groups were similar (46% vs 39%). The comparatively high response rate of bone metastases treated with RT alone and small sample size of our study might have confounded the additive effect of zoledronic acid on the shrinkage of bone metastases, however, and these results should accordingly be interpreted with caution.

The local progression rate of bone metastases from HCC at 6 months after RT has been reported as 53%.[25] In the present study, while the radiographic progression rate of irradiated bone metastases of the non-Z group at 6 months was 43%, radiographic progression of irradiated bone metastases of the Z group was not observed. The lack of a statistical difference ($P = 0.11$) was likely due to the small sample size. Although the radiographic response rate of non-irradiated bone metastases of the Z group was 0%, the disease control rate of non-irradiated metastases of the Z group (71%) was higher than that of the non-Z group (0%), with significance ($P = 0.002$). In addition, the radiographic progression rate of non-irradiated bone metastases of the Z group was lower than that of the non-Z group ($P = 0.009$).

In previous studies, radiographic response rates of bone metastases from lung cancer and renal cell carcinoma, at 9% and 13%, respectively, were not improved by zoledronic acid alone.[12,13] Similarly, in the present study, we could not confirm the effect of zoledronic acid on the improvement of radiographic response rates. However, our findings do demonstrate the potential of zoledronic acid in delaying the enlargement of bone metastases from HCC.

Safety profiles of zoledronic acid have been reported for single use and in combination with RT.[12–14,24] In our present study, we saw no significant adverse events in combination use. Given the wide use of RT for bone metastases from HCC, these safety profiles of combination therapy will be beneficial for HCC patients with bone metastases.

In conclusion, our study showed that zoledronic acid delays the pain progression of both irradiated and non-irradiated bone metastases from HCC, and delays the radiographic progression of non-irradiated bone metastases.

REFERENCES

1 Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24**: 2137–50.
2 Okita K. Management of hepatocellular carcinoma in Japan. *J Gastroenterol* 2006; **41**: 100–6.
3 Uka K, Aikata H, Takaki S *et al.* Pretreatment predictor of response, time to progression, and survival to intraarterial

5-fluorouracil/interferon combination therapy in patients with advanced hepatocellular carcinoma. *J Gastroenterol* 2007; **42**: 845–53.
4 Kamada K, Kitamoto M, Aikata H *et al.* Combination of transcatheter arterial chemoembolization using cisplatin-lipiodol suspension and percutaneous ethanol injection for treatment of advanced small hepatocellular carcinoma. *Am J Surg* 2002; **184**: 284–90.
5 Rossi S, Di Stasi M, Buscarini E *et al.* Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. *AJR Am J Roentgenol* 1996; **167**: 759–68.
6 Uka K, Aikata H, Takaki S *et al.* Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. *World J Gastroenterol* 2007; **13**: 414–20.
7 Natsuizaka M, Omura T, Akaike T *et al.* Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol* 2005; **20**: 1781–7.
8 Katyal S, Oliver JH III, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma. *Radiology* 2000; **216**: 698–703.
9 Seong J, Koom WS, Park HC. Radiotherapy for painful bone metastases from hepatocellular carcinoma. *Liver Int* 2005; **25**: 261–5.
10 He J, Zeng ZC, Tang ZY *et al.* Clinical features and prognostic factors in patients with bone metastases from hepatocellular carcinoma receiving external beam radiotherapy. *Cancer* 2009; **115**: 2710–20.
11 Kaizu T, Karasawa K, Tanaka Y *et al.* Radiotherapy for osseous metastases from hepatocellular carcinoma: a retrospective study of 57 patients. *Am J Gastroenterol* 1998; **93**: 2167–71.
12 Rosen LS, Gordon D, Kaminski M *et al.* Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003; **98**: 1735–44.
13 Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. *Cancer* 2003; **98**: 962–9.
14 Wardley A, Davidson N, Barrett-Lee P *et al.* Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomised, crossover study of community vs hospital bisphosphonate administration. *Br J Cancer* 2005; **92**: 1869–76.
15 Montella L, Addeo R, Palmieri G *et al.* Zoledronic acid in the treatment of bone metastases by hepatocellular carcinoma: a case series. *Cancer Chemother Pharmacol* 2010; **65**: 1137–43.
16 Chow E, Wu JS, Hoskin P, Coia LR, Bentzen SM, Blitzer PH. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Radiother Oncol* 2002; **64**: 275–80.
17 van der Linden YM, Lok JJ, Steenland E *et al.* Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys* 2004; **59**: 528–37.
18 Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.
19 Oken MM, Creech RH, Tormey DC *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55.
20 Dunford JE, Rogers MJ, Ebetino FH, Phipps RJ, Coxon FP. Inhibition of protein prenylation by bisphosphonates causes sustained activation of Rac, Cdc42, and Rho GTPases. *J Bone Miner Res* 2006; **21**: 684–94.
21 Zhang FL, Casey PJ. Protein prenylation: molecular mechanisms and functional consequences. *Annu Rev Biochem* 1996; **65**: 241–69.
22 Green JR. Antitumor effects of bisphosphonates. *Cancer* 2003; **97**: 840–7.
23 Arrington SA, Damron TA, Mann KA, Allen MJ. Concurrent administration of zoledronic acid and irradiation leads to improved bone density, biomechanical strength, and microarchitecture in a mouse model of tumor-induced osteolysis. *J Surg Oncol* 2008; **97**: 284–90.
24 Kijima T, Fujii Y, Suyama T *et al.* Radiotherapy to bone metastases from renal cell carcinoma with or without zoledronate. *BJU Int* 2009; **103**: 620–4.
25 Nakamura N, Igaki H, Yamashita H *et al.* A retrospective study of radiotherapy for spinal bone metastases from hepatocellular carcinoma (HCC). *Jpn J Clin Oncol* 2007; **37**: 38–43.

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SPECIAL FEATURE

Strategies of radiotherapy for recurrent and metastatic breast cancer

Management of locoregional recurrence of breast cancer

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Abstract The locoregional recurrence of breast cancer is not a sign of distant metastases, and a substantial proportion of cases are cured by salvage therapy. Patients with locoregional recurrence should not be treated with palliative intent as if they have visceral metastases. The recommended treatment for ipsilateral breast recurrence after breast conservative therapy is a mastectomy. For patients who suffer from isolated chest wall recurrence after mastectomy, a surgical approach is recommended. Neoadjuvant chemotherapy is considered for patients with unresectable disease in order to render the disease resectable. For patients with isolated chest wall recurrence who have received no prior radiotherapy, postoperative radiotherapy involving the chest wall and regional lymph nodes is recommended. Patients with isolated axillary lymph node recurrence should be treated with axillary dissection or resection. Although the effectiveness of systemic therapy for patients with locoregional recurrence is unclear, there is a trend toward treating patients with supraclavicular lymph node recurrence with radiotherapy plus systemic therapy. Pain relief and the eradication of other distressing symptoms resulting from inoperable disease are achieved in two-thirds to three-quarters of patients by radiotherapy with or without systemic therapy. New anticancer agents and molecular target therapies should be evaluated with the objective of improving the treatment outcome of patients with locoregional recurrence. A combination of approaches is required for treatment of patients with locoregional recurrence, and a multidisciplinary tumor board should be organized at each institute.

Keywords Local recurrence · Lymph node recurrence · Radiotherapy · Chemotherapy · Mastectomy

Introduction

Ten to thirteen percent of patients who receive breast conservative therapy develop locoregional recurrence within 10 years of their initial treatment, and three to eight percent of patients who receive mastectomy plus postoperative radiotherapy will also develop locoregional recurrence [1]. The omission of postoperative radiotherapy increases the risk of ipsilateral breast recurrence or chest wall recurrence threefold. Ipsilateral breast recurrence after breast conservative therapy sometimes occurs after more than 10 years; however, approximately 80% of locoregional recurrences after mastectomy arise within the first 5 years [1–3]. The standard of care for locoregional recurrence has not been clarified because of its heterogeneous biological characteristics and a lack of well-designed prospective clinical trials. The authors have strived to assess the effectiveness of treatment strategies developed in previous studies.

Diagnosis and re-staging

The first step for choosing an appropriate treatment is pathological evaluation of the recurrent disease, and fine needle biopsy, core needle biopsy, and/or open biopsy can

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be used for this. The pathological subtype, histological grade, expression of hormonal receptors, and human epidermal growth factor receptor type2 (HER-2) overexpression should be evaluated when choosing appropriate treatment strategies for patients with recurrent disease. Radiation-induced sarcomas in the chest wall appear at a median of 10 years after postoperative treatment, but the latency period varies. The next step is a staging evaluation. Systemic disease can be carefully evaluated by using blood tests, chest computed tomography (CT), abdominal CT, pelvic CT, and radionuclide bone scans. Magnetic resonance imaging (MRI), CT, and color Doppler ultrasonography are useful for evaluating the extent of supraclavicular and infraclavicular lymph node recurrence. Positron emission tomography (PET) scans are performed increasingly in clinical practice and are more sensitive than CT and bone scans; however, meta-analysis of evaluation of breast cancer recurrence demonstrated that the false positive rate of PET scans was relatively high (11%) [4]. The clinical value of PET scans alone is not satisfactory, so addition of other conventional imaging modalities is required.

Prognostic factors

For patients with locoregional recurrence after breast conservative therapy, disease-free interval (DFI) from the initial treatment to recurrence is the most powerful predictive factor. The 5-year survival rate of patients who developed recurrence within 2 years of the initial treatment was 65% and that of the patients who developed recurrence after 2 years was over 80% [5]. Other poor prognostic factors of mortality have been reported, for example age (≥60 years), the number of positive lymph nodes at the initial treatment (four or more), primary tumor size (≥2 cm), histology (invasive cancer), and estrogen receptor expression (negative) [6]. For patients with locoregional recurrence after mastectomy, some tumor characteristics at the diagnosis of recurrence, for example an operable tumor, the absence of tumor necrosis, the recurrent site (chest wall or axillary lymph node), a pT1-2N0 primary tumor, and a long DFI, are associated with a good treatment outcome [7–9].

Schmoor et al. [9] reviewed 337 patients with locoregional recurrence among the 2,746 patients who received conservative therapy or mastectomy in four prospective studies of the German Breast Cancer Study Group. Multivariate analysis demonstrated that number of positive lymph nodes, tumor grade, estrogen receptor, and DFI were independent prognostic factors for progression-free survival after locoregional recurrence. They simplified the risk strata and defined three risk groups:

- low risk: primary node-negative status and a DFI of more than 2 years;
- intermediate risk: primary node-positive status or a DFI of more than 2 years; and
- high risk: primary node-positive status and a DFI of less than 2 years (Table 1).

Although it excludes other prognostic factors, for example age, tumor grade, recurrent site, and estrogen receptor, this simplified prognostic index is a useful tool for choosing treatment strategies in clinical practice and clinical trials.

Recurrence after breast conservative therapy

Thirteen percent of patients who develop recurrence after conservative therapy have locoregional recurrence alone, 30% have locoregional recurrence with distant metastases, and another 57% have distant metastases alone [2]. Approximately 80% of patients with locoregional recurrence develop ipsilateral breast recurrence as the first site [10, 11]. Recurrence in the ipsilateral breast includes two different types of disease, true recurrence and second primary tumors. True recurrence occurs within the primary tumor site or its vicinity, and second primary tumors occur in other quadrants of the breast or have a different pathological subtype [10, 12, 13]. However, some second primary tumors may occur in the same quadrant, and others will have the same pathological subtype. Strict distinction between true recurrence and second primary tumors is difficult, and some investigators have distinguished between them by using pathological subtype, location, and deoxyribonucleic acid (DNA) flow cytometry [10, 12, 13]. True recurrence is associated with early development (median interval: 3.7 vs. 7.3 years) and poor treatment outcome (10-year overall survival: 55 vs. 75%) compared with second primary tumors [12].

Table 1 Prognostic index for patients with locoregional recurrence of breast cancer [9]

	5-year PFS (95%CI)	5-year OS (95%CI)
Low risk		
Node (−) and DFI ≦2 years	53% (41–64)	66% (55–77)
Intermediate risk		
Node (+) or DFI >2 years	40% (31–49)	53% (44–62)
High risk		
Node (+) and DFI >2 years	17% (9–25)	27% (17–36)

Node (−), primary node-negative status; DFI, disease-free interval from initial treatment to recurrence; Node (+), primary node-positive status; PFS, progression-free survival; OS, overall survival; 95%CI, 95% confidence interval

Ipsilateral breast recurrence after breast conservative therapy

More than 20% of evaluated mastectomy specimens of ipsilateral breast recurrence after conservative therapy revealed substantial residual disease in two or more quadrants of the breast [14]. The generally recommended treatment for ipsilateral breast recurrence after breast conservative therapy is salvage mastectomy with or without axillary dissection [5, 6, 14–17]. Approximately 90% of the patients have operable recurrent tumors, and other patients have inoperative tumors with diffuse infiltration or inflammatory changes [11, 14–16, 18]. Most patients who received salvage mastectomy achieved good local control, and the 5-year overall survival rates after recurrence ranged from 60 to 86% [5, 6, 12, 14, 18]. Patients who have inoperative tumors involving diffuse infiltration or inflammatory changes have a poor prognosis [19].

Less intensive salvage care for locoregional recurrence has also been investigated. Several investigators have reported the outcome of repeated conservative therapy including partial breast resection with or without radiotherapy after ipsilateral breast recurrence [16, 18, 20]. Salvadori et al. [18] reported the same overall survival in patients who underwent re-conservative therapy (85%) and patients who received salvage mastectomy (70%); however, second ipsilateral recurrence was more common in the patients who received re-conservative therapy (19 vs. 4%). Galper et al. [16] reviewed 341 patients with local recurrence after conservative therapy and reported that the time to distant failure, second malignancy, or death of the patients who received re-conservative therapy was worse than that of the patients who received salvage mastectomy (hazard ratio: 2.0, $p = 0.02$). Re-conservative therapy for ipsilateral breast recurrence is not recommended. Sentinel lymph node (SLN) biopsy is a less toxic tool, and the experience of the Memorial Sloan–Kettering Cancer Center demonstrated that SLN were identified in 55% of 117 patients who had undergone prior axillary dissection or biopsy. Although SLN biopsy is available for some patients who have undergone prior axillary dissection, further studies are required [21].

Postoperative radiotherapy after salvage mastectomy is used for patients with a positive surgical margin or macroscopic residual tumor who have no history of breast irradiation. Re-irradiation is associated with late adverse effects such as tissue necrosis, fibrosis, and rib fractures. There are no data supporting prophylactic regional lymph node irradiation after salvage mastectomy for patients with ipsilateral breast recurrence.

Only one randomized clinical trial has evaluated addition of tamoxifen (TAM) for patients who underwent complete resection and postoperative radiotherapy [22]. Although the addition of TAM prolonged relapse-free survival, 9-year overall survival did not improve. Le et al. [23] reported that systemic chemotherapy and hormonal therapy reduced the risk of death for premenopausal patients, but did not reduce it for postmenopausal patients. Cochran's systematic review concluded that there was little evidence to support the addition of systemic therapy for patients with locoregional recurrence of breast cancer [24]. However, the addition of hormonal therapies is considered to be reasonable in selected patients because of their limited toxicities [25].

Regional lymph nodes recurrence after breast conservative therapy

Regional lymph node recurrence after breast conservative therapy is relatively rare (0.5–6.3%) [6, 26, 27]. The most common sites of regional recurrence are the axillary area and supraclavicular fossa [28, 29]. The pooled analyses of the National Surgical Adjuvant Breast and Bowel Project studies demonstrated that the prognosis of patients with isolated axillary lymph node recurrence was more favorable than that of patients with supraclavicular lymph node recurrence, and the 5-year distant metastases-free survival of the former was 31.5% whereas that of the latter was only 12.1% [6].

The experience of the MD Anderson Cancer Center was that surgery for axillary recurrence achieved good local control; however, the absence of radiotherapy or systemic therapy from the multimodality treatment strategy did not correlate with disease control or the frequency of distant metastases [30]. Maximum axillary control is achieved with an axillary dissection whenever feasible. Limited data are available regarding postoperative regional lymph node irradiation [28]. Radiotherapy is indicated for patients who undergo incomplete resection of axillary disease and patients with supraclavicular lymph nodes metastases [29]. Although the role of systemic therapy has not been established, there is a trend towards administering systemic therapy to patients with supraclavicular lymph nodes recurrence [17].

Fowble et al. [27] reported that none of their six patients with isolated axillary recurrence subsequently developed breast recurrence. They also concluded that isolated axillary node recurrence without clinical or mammographic evidence of ipsilateral breast recurrence does not require a prophylactic mastectomy.

Recurrence after mastectomy

According to the pooled analysis of the Easton Cooperative Oncology Group, locoregional recurrence developed in 420

patients among 2,016 patients who received mastectomy and adjuvant systemic therapy without postoperative radiotherapy [31]. Among 254 patients without simultaneous distant metastasis, isolated chest wall recurrence was found in 131 patients (52%), and locoregional recurrence with or without chest wall recurrence was found in 123 patients (48%). One hundred and sixty-six patients had locoregional recurrence and distant metastases simultaneously.

Isolated chest wall recurrence after mastectomy

Maximum local control of isolated chest wall recurrence is achieved with a wide excision whenever feasible [32–37]. Schwaibold et al. [36] reviewed 128 patients with isolated locoregional recurrence and reported that the 5-year overall survival and relapse-free survival rates of patients with a long DFI, surgical resection, and locoregional control were 61 and 59%, respectively. However, this favorable subgroup accounted for fewer than 20% of patients with isolated locoregional recurrence. On the other hand, aggressive surgery including extensive excision and reconstruction using skin grafts leads to a reduced quality of life, and, therefore, optimum treatment is achieved by balancing the potential benefits of local treatment with its adverse effects [38, 39]. If there is no clinical finding of axillary lymph node involvement, a prophylactic axillary dissection is unnecessary for patients who have undergone prior complete axillary dissection. The identification of SLN after prior axillary dissection is unlikely to be as successful as prior SLN biopsy alone (38 vs. 74%, $p = 0.0002$), and so SLN biopsy is not recommended for patients who have undergone prior complete axillary dissection [21].

Dahlstrom et al. [32] reported that 45% of patients had a new local recurrence after wide excision plus a 3-cm margin for isolated chest wall recurrence. In the study by Mallinckrodt, the 5-year freedom from chest wall re-recurrence of patients who received entire chest wall and regional lymph node irradiation was 75%, and that of patients who received small-field irradiation alone was 36% ($p = 0.0001$) [7]. Toonkel et al. [40] demonstrated that postoperative radiotherapy including chest wall and regional lymph node irradiation enhanced 5-year overall survival rates compared with chest wall irradiation alone (54 vs. 27%). The three-field or four-field technique including tangential chest wall fields and an en face supraclavicular area field are usually applied, even if the recurrent disease involves an isolated chest wall recurrence [32, 34, 36, 40–42]. The optimum daily fraction size is 1.8–2.0 Gy, and should be delivered five times weekly. The total dose administered to the initial field ranges from 45 to 50 Gy, with a boost of 10 to 20 Gy administered to areas of residual gross disease and the tumor bed. The biopsy scar should be covered by the bolus in order to obtain the optimum dose distribution [25]. In the MD Anderson Cancer Center, all areas treated prophylactically receive 54 Gy in 27 fractions, and all areas to be boosted because of microscopic disease receive an additional 12 Gy in 6 fractions [43].

A higher dose of definitive radiation for macroscopically residual tumors is associated with less in-field failure [7, 25]. It is difficult to obtain long-term local control in patients with diffuse inflammatory disease or unresectable disease. Neoadjuvant chemotherapy is considered for patients with unresectable disease in order to render the disease resectable, and radiotherapy is delivered after surgery. There is little information about re-irradiation after postoperative chest wall irradiation. Limited field re-irradiation using tailored conformal therapy techniques and concurrent chemoradiotherapy and/or twice daily fractionation regimens have been tested for patients with inoperative recurrent disease who had previously received radiotherapy [44, 45]. Re-irradiation of limited volumes with limited radiation doses can result in meaningful palliation for some patients.

Regional lymph nodes recurrence after mastectomy

Willner et al. [34] analyzed 145 patients with first locoregional recurrences after mastectomy and reported that the 5-year survival rate was better for patients with recurrences confined to the axillary lymph nodes (50%) than for those with recurrence confined to the supraclavicular lymph nodes (28%) or combined chest wall and axillary recurrences (28%). The 5-year survival rate of patients with supraclavicular lymph nodes recurrence and chest wall and/or axillary lymph nodes recurrence was only 5%.

Axillary lymph node recurrence after mastectomy

Axillary lymph node recurrence is rare after complete axillary dissection. Regional lymph node control for patients who receive axillary dissection after axillary recurrence is better than that for patients who receive radiotherapy alone [42]. Whenever feasible, a complete axillary dissection (Level I and II) is indicated for patients who have undergone prior SLN biopsy alone, and gross tumor resection is considered for patients who have undergone prior complete axillary dissection. Although the role of postoperative radiotherapy after salvage surgery is unclear, postoperative radiotherapy is used for patients who have not undergone prior axillary irradiation in some institutes [33, 34, 42, 46]. Radiotherapy should be considered for patients with incompletely resected disease or inoperable disease. The risk of symptomatic arm edema

after axillary dissection or axillary irradiation alone ranged from 4 to 8%; that after complete axillary dissection followed by radiotherapy was 36%, however [47].

Supraclavicular lymph node recurrence after mastectomy

Chen et al. [48] reviewed 63 patients with isolated supraclavicular lymph node recurrence among 3,170 breast cancers and reported that their 5-year survival rate was 33.6% and that surgical removal of the supraclavicular lymph nodes was associated with good overall survival after recurrence ($p = 0.03$). Although a surgical approach for supraclavicular lymph node recurrence is feasible, the clinical benefit of a surgical approach is believed to be small, because of the high frequency of local and distant relapse [49].

The clinical complete response rate for radiotherapy with or without chemotherapy ranged from 85 to 94%, the median time to progression was 28 months, and the 5-year overall survival rate after recurrence ranged from 21 to 35% [34, 46, 50]. Pergolizzi [51] compared 18 patients who received six-cycle chemotherapy alone with 19 patients who received initial three-cycle chemotherapy followed by involved-field radiotherapy and demonstrated that the local control of the former patients was worse than that of the latter patients (13 patients vs. 18 patients) and that the 5-year disease-free survival rate of the former was worse than that of the latter (5.5 vs. 21%, $p = 0.01$). Although there are no data supporting the use of systemic therapy for patients with locoregional recurrence, there is a trend toward the application of systemic therapy especially for patients with supraclavicular recurrence [23, 24, 34, 46].

Tumor infiltration of the brachial plexus induces shoulder pain, sensory changes in the fingers, and weakness and atrophy of the upper limbs. Radiation therapy is an effective local therapy for obtaining local control and avoiding distressing symptoms. Doses of 30–50 Gy are applied in 10–25 fractions over 2–5 weeks, and pain relief and the eradication of other distressing symptoms were achieved in more than two-thirds of patients [46, 50, 52]. Doses of 40 Gy or more were better at improving the distressing symptoms caused by supraclavicular lymph node metastases than those of less than 40 Gy (92 vs. 55%) [52].

New challenge

The 5-year overall survival rates of patients with ipsilateral breast or chest wall recurrence with simultaneous regional lymph node recurrence range from 7 to 24% [6, 34, 46]. Although systemic therapy has been commonly applied for patients with locoregional recurrence, the clinical benefit of systemic therapy including anthracycline-based and methotrexate-based regimens is uncertain. The clinical data regarding taxane-based regimens and molecular-targeted therapies, for example trastuzumab and lapatinib, should be evaluated using prospective trials, and a pilot study using hyperfractionated accelerated radiotherapy with or without systemic therapy has been conducted [44]. Additionally, patients with diffuse inflammatory disease and unresectable disease have an unfavorable prognosis. The optimum treatment for unresectable diffuse inflammatory recurrent disease needs to be established.

Locoregional recurrences of breast cancer have heterogeneous biological characteristics, and it is difficult to choose an appropriate treatment for each patient. Prospective clinical trials integrating adequate prognostic indices should therefore be conducted to define standard salvage treatment for patients with locoregional recurrence [9].

Conclusion

The optimum treatment for patients with locoregional recurrence requires a combination of modalities, and a comprehensive multidisciplinary treatment approach is essential. A multidisciplinary tumor board for breast cancer should be organized at each institute in order to propose an appropriate treatment for each patient.

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References

1. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087–106.
2. van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst. 2000;92(14):1143–50.
3. Buchanan CL, Dorn PL, Fey J, Giron G, Naik A, Mendez J, et al. Locoregional recurrence after mastectomy: incidence and outcomes. J Am Coll Surg. 2006;203(4):469–74.

4. Isasi CR, Moadel RM, Blaufox MD. A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases. Breast Cancer Res Treat. 2005;90(2):105–12.
5. Doyle T, Schultz DJ, Peters C, Harris E, Solin LJ. Long-term results of local recurrence after breast conservation treatment for invasive breast cancer. Int J Radiat Oncol Biol Phys. 2001;51(1):74–80.
6. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol. 2006;24(13):2028–37.
7. Halverson KJ, Perez CA, Kuske RR, Garcia DM, Simpson JR, Fineberg B. Isolated local-regional recurrence of breast cancer following mastectomy: radiotherapeutic management. Int J Radiat Oncol Biol Phys. 1990;19(4):851–8.
8. Chagpar A, Kuerer HM, Hunt KK, Strom EA, Buchholz TA. Outcome of treatment for breast cancer patients with chest wall recurrence according to initial stage: implications for post-mastectomy radiation therapy. Int J Radiat Oncol Biol Phys. 2003;57(1):128–35.
9. Schmoor C, Sauerbrei W, Bastert G, Schumacher M. Role of isolated locoregional recurrence of breast cancer: results of four prospective studies. J Clin Oncol. 2000;18(8):1696–708.
10. Freedman GM, Anderson PR, Hanlon AL, Eisenberg DF, Nicolaou N. Pattern of local recurrence after conservative surgery and whole-breast irradiation. Int J Radiat Oncol Biol Phys. 2005;61(5):1328–36.
11. Leborgne F, Leborgne JH, Ortega B, Doldan R, Zubizarreta E. Breast conservation treatment of early stage breast cancer: patterns of failure. Int J Radiat Oncol Biol Phys. 1995;31(4):765–75.
12. Smith TE, Lee D, Turner BC, Carter D, Haffty BG. True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. Int J Radiat Oncol Biol Phys. 2000;48(5):1281–9.
13. Huang E, Buchholz TA, Meric F, Krishnamurthy S, Mirza NQ, Ames FC, et al. Classifying local disease recurrences after breast conservation therapy based on location and histology: new primary tumors have more favorable outcomes than true local disease recurrences. Cancer. 2002;95(10):2059–67.
14. Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. Int J Radiat Oncol Biol Phys. 1990;19(4):833–42.
15. Abner AL, Recht A, Eberlein T, Come S, Shulman L, Hayes D, et al. Prognosis following salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stage breast cancer. J Clin Oncol. 1993;11(1):44–8.
16. Galper S, Blood E, Gelman R, Abner A, Recht A, Kohli A, et al. Prognosis after local recurrence after conservative surgery and radiation for early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2005;61(2):348–57.
17. Huston TL, Simmons RM. Locally recurrent breast cancer after conservation therapy. Am J Surg. 2005;189(2):229–35.
18. Salvadori B, Marubini E, Miceli R, Conti AR, Cusumano F, Andreola S, et al. Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. Br J Surg. 1999;86(1):84–7.
19. Gage I, Schnitt SJ, Recht A, Abner A, Come S, Shulman LN, et al. Skin recurrences after breast-conserving therapy for early-stage breast cancer. J Clin Oncol. 1998;16(2):480–6.
20. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG. Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. Int J Radiat Oncol. Biol Phys. 2005;63(3):845–51.
21. Port ER, Garcia-Etienne CA, Park J, Fey J, Borgen PI, Cody HS 3rd. Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence. Ann Surg Oncol. 2007;14(8):2209–14.
22. Borner M, Bacchi M, Goldhirsch A, Greiner R, Harder F, Castiglione M, et al. First isolated locoregional recurrence following mastectomy for breast cancer: results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. Swiss Group for Clinical Cancer Research. J Clin Oncol. 1994;12(10):2071–7.
23. Le MG, Arriagada R, Spielmann M, Guinebretiere JM, Rochard F. Prognostic factors for death after an isolated local recurrence in patients with early-stage breast carcinoma. Cancer. 2002;94(11):2813–20.
24. Rauschecker H, Clarke M, Gatzemeier W, Recht A. Systemic therapy for treating locoregional recurrence in women with breast cancer. Cochrane Database Syst Rev. 2001; (4):CD002195.
25. Recht A, Hayes DF, Eberlein TJ, Sadowsky NL. Local-regional recurrence after mastectomy or breast-conserving therapy. Philadelphia: Lippincott–Raven; 1996.
26. Fodor J, Toth J, Major T, Polgar C, Nemeth G. Incidence and time of occurrence of regional recurrence in stage I-II breast cancer: value of adjuvant irradiation. Int J Radiat Oncol Biol Phys. 1999;44(2):281–7.
27. Fowble B, Solin LJ, Schultz DJ, Goodman RL. Frequency, sites of relapse, and outcome of regional node failures following conservative surgery and radiation for early breast cancer. Int J Radiat Oncol Biol Phys. 1989;17(4):703–10.
28. Lukens JN, Vapiwala N, Hwang WT, Solin LJ. Regional nodal recurrence after breast conservation treatment with radiotherapy for women with early-stage breast carcinoma. Int J Radiat Oncol Biol Phys. 2009;73(5):1475–81.
29. Harris EE, Hwang WT, Seyednejad F, Solin LJ. Prognosis after regional lymph node recurrence in patients with stage I-II breast carcinoma treated with breast conservation therapy. Cancer. 2003;98(10):2144–51.
30. Newman LA, Hunt KK, Buchholz T, Kuerer HM, Vlastos G, Mirza N, et al. Presentation, management and outcome of axillary recurrence from breast cancer. Am J Surg. 2000;180(4):252–6.
31. Recht A, Gray R, Davidson NE, Fowble BL, Solin LJ, Cummings FJ, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. J Clin Oncol. 1999;17(6):1689–700.
32. Dahlstrom KK, Andersson AP, Andersen M, Krag C. Wide local excision of recurrent breast cancer in the thoracic wall. Cancer. 1993;72(3):774–7.
33. Clemons M, Hamilton T, Mansi J, Lockwood G, Goss P. Management of recurrent locoregional breast cancer: oncologist survey. Breast. 2003;12(5):328–37.
34. Willner J, Kiricuta IC, Kolbl O. Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. Int J Radiat Oncol Biol Phys. 1997;37(4):853–63.
35. Haylock BJ, Coppin CM, Jackson J, Basco VE, Wilson KS. Locoregional first recurrence after mastectomy: prospective cohort studies with and without immediate chemotherapy. Int J Radiat Oncol Biol Phys. 2000;46(2):355–62.
36. Schwaibold F, Fowble BL, Solin LJ, Schultz DJ, Goodman RL. The results of radiation therapy for isolated local regional recurrence after mastectomy. Int J Radiat Oncol Biol Phys. 1991;21(2):299–310.
37. Aberizk WJ, Silver B, Henderson IC, Cady B, Harris JR. The use of radiotherapy for treatment of isolated locoregional

recurrence of breast carcinoma after mastectomy. Cancer. 1986;58(6):1214–8.
38. Faneyte IF, Rutgers EJ, Zoetmulder FA. Chest wall resection in the treatment of locally recurrent breast carcinoma: indications and outcome for 44 patients. Cancer. 1997;80(5):886–91.
39. Salvadori B, Rovini D, Squicciarini P, Conti R, Cusumano F, Grassi M. Surgery for local recurrences following deficient radical mastectomy for breast cancer: a selected series of 39 cases. Eur J Surg Oncol. 1992;18(5):438–41.
40. Toonkel LM, Fix I, Jacobson LH, Wallach CB. The significance of local recurrence of carcinoma of the breast. Int J Radiat Oncol Biol Phys. 1983;9(1):33–9.
41. Bedwinek JM, Lee J, Fineberg B, Ocwieza M. Prognostic indicators in patients with isolated local-regional recurrence of breast cancer. Cancer. 1981;47(9):2232–5.
42. Kuo SH, Huang CS, Kuo WH, Cheng AL, Chang KJ, Chia-Hsien Cheng J. Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiat Oncol Biol Phys. 2008;72(5):1456–64.
43. Tereffe W, Strom EA. Radiation therapy for early and advanced breast cancer. 2nd ed. New York: Springer; 2008.
44. Ballo MT, Strom EA, Prost H, Singletary SE, Theriault RL, Buchholz TA, et al. Local-regional control of recurrent breast carcinoma after mastectomy: does hyperfractionated accelerated radiotherapy improve local control? Int J Radiat Oncol Biol Phys. 1999;44(1):105–12.
45. Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, et al. Multi-institutional review of repeat irradiation of chest wall and breast for recurrent breast cancer. Int J Radiat Oncol Biol Phys. 2008;70(2):477–84.
46. Recht A, Pierce SM, Abner A, Vicini F, Osteen RT, Love SM, et al. Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol. 1991;9(6):988–96.
47. Larson D, Weinstein M, Goldberg I, Silver B, Recht A, Cady B, et al. Edema of the arm as a function of the extent of axillary surgery in patients with stage I-II carcinoma of the breast treated with primary radiotherapy. Int J Radiat Oncol Biol Phys. 1986;2(9):1575–82.
48. Chen SC, Chang HK, Lin YC, Leung WM, Tsai CS, Cheung YC, et al. Prognosis of breast cancer after supraclavicular lymph node metastasis: not a distant metastasis. Ann Surg Oncol. 2006;13(11):1457–65.
49. Veronesi G, Scanagatta P, Leo F, Petrella F, Galetta D, Gasparri R, et al. Subclavicular recurrence of breast cancer: does surgery play a role? Breast. 2006;15(5):649–53.
50. Pergolizzi S, Adamo V, Russi E, Santacaterina A, Maisano R, Numico G, et al. Prospective multicenter study of combined treatment with chemotherapy and radiotherapy in breast cancer women with the rare clinical scenario of ipsilateral supraclavicular node recurrence without distant metastases. Int J Radiat Oncol Biol Phys. 2006;65(1):25–32.
51. Pergolizzi S, Settineri N, Santacaterina A, Spadaro P, Maisano R, Caristi N, et al. Ipsilateral supraclavicular lymph nodes metastases from breast cancer as only site of disseminated disease. Chemotherapy alone vs. induction chemotherapy to radical radiation therapy. Ann Oncol. 2001;12(8):1091–5.
52. Ampil FL, Caldito G, Li BD, Burton GV. Supraclavicular nodal relapse of breast cancer: prevalence, palliation, and prognosis. Eur J Gynaecol Oncol. 2003;24(3–4):233–5.

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Recording of morbidity

Validation of the Total Dysphagia Risk Score (TDRS) as a predictive measure for acute swallowing dysfunction induced by chemoradiotherapy for head and neck cancers

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ABSTRACT

Background and purpose: Methods for predicting acute swallowing dysfunction in patients with head and neck cancers undergoing definitive chemoradiotherapy have not been established. We investigated the validity of the Total Dysphagia Risk Score (TDRS) as a predictive measure for this morbidity.

Materials and methods: Forty-seven patients with head and neck cancers who underwent definitive chemoradiotherapy between December 1998 and March 2006 were reviewed retrospectively. Median age was 63 years (range, 16–81). Almost all patients underwent platinum-based concomitant chemoradiotherapy. Factors of the TDRS were as follows: T-classification, neck irradiation, weight loss, primary tumour site and treatment modality. Patients were classified into three risk groups according to the TDRS.

Results: Swallowing dysfunction was observed in 27 patients (57%) as RTOG grade 2 or higher acute morbidity. This classification was significantly associated with grade 2 or higher acute swallowing dysfunction ($P < 0.001$). In ROC (receiver operator characteristic) analysis, the cut-off value of TDRS was set at 18 (sensitivity = 0.81; specificity = 0.85). Prediction of severe (grade $\geqslant 3$) acute swallowing dysfunction was similarly obtained.

Conclusion: The TDRS is a useful tool to predict acute swallowing dysfunction induced by chemoradiotherapy for head and neck cancers.

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Definitive chemoradiotherapy is now a widely accepted treatment option for patients with head and neck cancers. In recent years, it has been revealed that addition of concomitant chemotherapy to radiotherapy not only improves the outcome but also increases toxicity of the treatment. Rosenthal et al. reported that 40–70% of patients undergoing concomitant chemoradiotherapy for head and neck cancers experienced severe mucositis and 50–80% required feeding tube placement during the course of therapy [1]. Severe swallowing dysfunction arising during the course of therapy reduces the patient's quality of life and adversely affects their physical condition. Prediction of this morbidity may facilitate prophylactic intervention and prevention of these adverse effects [2], but accurate predictive methods have not been established.

Recently, Langendijk et al. advocated a simple measure designated as the Total Dysphagia Risk Score (TDRS) to predict swallowing dysfunction after curative radiotherapy for head and neck cancers [3]. They also reported that this predictive model could also be adapted for acute morbidity. Here, a retrospective review of patients with head and neck cancers who underwent definitive chemoradiotherapy in our facility was performed to investigate the validity of the TDRS as a predictive measure for acute swallowing dysfunction in these patients.

Materials and methods

Between December 1998 and March 2006, 47 patients with head and neck cancers underwent definitive chemoradiotherapy at our facility. The patients' characteristics are shown in Table 1. In our facility, definitive chemoradiotherapy is usually performed in patients with good performance status, with no distant metastasis and 75 years old or less.

All except two patients underwent platinum-based concomitant chemoradiotherapy; the two exceptions were treated by radiotherapy and docetaxel-alone chemotherapy, respectively. Various chemotherapy regimens were adopted (Table 2). As we had been searching for the optimal chemotherapy regimen for several years and the method of therapy had consequently changed over that time, the chemotherapeutic agents used in the cases included in the present study were heterogeneous. The cumulative dose of *cis*-diamminedichloroplatinum (cisplatin) ranged from 80 mg/m^2 to 300 mg/m^2 (median, 100 mg/m^2). 5-Fluorouracil (5-FU) was administered to 43 patients. The cumulative dose of

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Table 1
Patient characteristics.

Characteristics		Number of patients
Gender	Male	41
	Female	6
Age		16–81 (median: 63)
Performance status	0	44
	⩾1	3
T-classification	T2	24
	T3–T4	23
Stage	II	20
	III	6
	IV	21
Primary site	Larynx	18
	Oropharynx	11
	Nasopharynx	7
	Hypopharynx	7
	Nasal cavity	2
	Oral cavity	2
Histology	Squamous cell carcinoma	47
Chemotherapy	Platinum-based	45
	Docetaxel alone	2
Radiation schedule	Conventional fractionation	41
	Hyperfractionation	6
Neck irradiation	Local or unilateral	20
	Bilateral	27
Weight loss (baseline)	No weight loss	36
	1–10%	10
	>10%	1

Table 2
Chemotherapy regimens.

Chemotherapy agents	Number of patients
Cisplatin (10 mg/m^2 on days 36–40, 43–47) + 5-FU (400 mg/m^2 on days 36–40, 43–47)	26
Cisplatin (50 mg/m^2 on days 6–7, 41–42, 71–72) + 5-FU (800 mg/m^2 on days 1–5, 36–40, 43–47)	9
Cisplatin (80 mg/m^2 on day 29) + 5-FU (400 mg/m^2 on days 29–33)	5
Others	7

5-FU ranged from 2000 mg/m^2 to 12,000 mg/m^2 (median 4000 mg/m^2).

In radiation therapy, casts for immobilisation and a photon beam of 4 MV were used in all patients. The fraction size was 1.5–2.0 Gy. The total dose of radiation therapy ranged from 50–70 Gy, and the median dose was 70 Gy. As various treatment protocols with different fraction sizes and total doses had been used in our facility, we also calculated the biologically effective dose (BED) in a linear-quadratic model [4]. BED was defined as $nd(1 + d/\alpha/\beta)$, with units of Gy, where n is the fractionation number, d is the daily dose and α/β was assumed to be 10 for tumours and acute toxicity. The BED ranged from 60 to 84 Gy (median 84 Gy). Forty-one patients received a once-daily fractionation schedule and six patients were treated with a partially accelerated hyperfractionation schedule. In this schedule, patients initially received 40 Gy in once-daily fractionation with a fraction size of 2 Gy. Subsequently, radiation field size was reduced to avoid the spinal cord and 30 Gy was added in twice-daily fractionation with a fraction size of 1.5 Gy. Lateral opposing portals alone or lateral opposing and anterior portals (3-field approach) were used according to the individual tumour spread. Stage II disease was usually treated by locally confined portals. The whole (bilateral) neck was usually included in the treatment of stage III–IV disease initially. The spinal cord was usually avoided by cone-down field reduction after administration of 40 Gy. CT images for radiation dose distribution were attained in 14 patients. None of the patients underwent intensity-modulated radiation therapy. Overall treatment time ranged from 31 to 109 days (median, 50 days).

Morbidity was retrospectively assessed using medical records, and scored by the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria [5]. In these criteria, grade 2 swallowing dysfunction is defined as moderate dysphagia and/or odynophagia, which may require narcotic analgesics and/or pureed or liquid diet. Grade 3 is defined as severe dysphagia or odynophagia with dehydration or weight loss requiring naso-gastric feeding tube, intravenous fluids or hyperalimentation. The TDRS is a summation of the following risk points: T-classification (T3 = 4 points; T4 = 4 points), neck irradiation (bilateral neck irradiation = 9 points), weight loss (1–10% = 5 points; >10% = 7 points), primary tumour site (oropharynx = 7 points; nasopharynx = 9 points) and treatment modality (accelerated radiotherapy = 6 points; concomitant chemotherapy = 5 points). The definition used in this study was identical to that of Langendijk et al. [3]. In the present study, patients who underwent partially accelerated radiation therapy were not allocated to 6 points. Accordingly, the risk points of treatment modality were set at 5 in all patients. The patients were divided into a low risk group (TDRS = 0–9), intermediate risk group (TDRS = 10–18) and high risk group (TDRS > 18).

Statistical analyses were performed using the χ^2 test, and $P < 0.05$ was taken to indicate statistical significance. ROC (receiver operator characteristic) curves were also plotted to evaluate the predictive capability of TDRS for grade 2 or higher acute swallowing dysfunction.

These analyses were performed using the statistical software JMP version 5.1.1 (SAS Institute Inc., Cary, NC, USA).

Results

Grade 2 or higher swallowing dysfunction was observed in 27 patients (57%) as an acute morbidity. Of those, severe (grade ⩾ 3) dysfunction occurred in 22 patients (81%). The results of classification into three risk groups according to TDRS and the relationship between the risk groups and RTOG grade are shown in Table 3. This classification was significantly associated with both grade ⩾ 2 and grade ⩾ 3 acute swallowing function. The ROC curve was plotted to evaluate the prediction capability of TDRS for grade ⩾ 2 acute swallowing dysfunction (Fig. 1). The cut-off value was set at 18 (sensitivity = 0.81; specificity = 0.85), which was consistent with the borderline between the intermediate and high risk groups. Accuracy for prediction was moderate (area under the curve = 0.80). Almost the same accuracy was obtained when grade ⩾ 3 acute swallowing dysfunction was defined as positive (area under the curve = 0.83). The cut-off value was also set at 18 (sensitivity = 0.86; specificity = 0.76).

The median duration of severe (grade ⩾ 3) swallowing dysfunction was 53 days (range, 21–142 days). To manage the severe swallowing dysfunction, total parenteral nutrition was usually adopted at our facility. Enteral feeding was not usually adopted. Seventeen

Table 3
Relationships between the three risk groups and grading of swallowing dysfunction in RTOG Acute Radiation Morbidity Scoring Criteria.

Risk groups	Total	RTOG grade		
		0–1	⩾2	⩾3
Low	16	13 (81%)	3 (19%)	1 (6%)
Intermediate	9	4 (44%)	5 (56%)	4 (44%)
High	22	3 (14%)	19 (86%)	17 (77%)
Total	47	20 (43%)	27 (57%)	22 (47%)

The differences were statistically significant ($P < 0.001$; degrees of freedom = 2) in both grade ⩾ 2 and grade ⩾ 3 acute swallowing dysfunction.

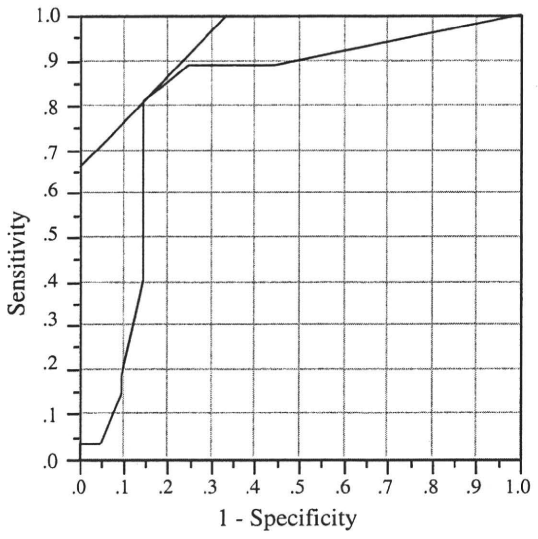

Fig. 1. ROC (receiver operator characteristic) curve to evaluate the prediction capability of the TDRS for grade 2 or higher acute swallowing dysfunction.

patients required total parenteral nutrition. No patients in the low risk group and three patients (33%) in the intermediate risk group required this procedure. In contrast, 14 patients (64%) in the high risk group required this procedure. Median duration of hospitalization after termination of treatment in the low, intermediate, and high risk group was 15 days (range, 1–31), 26 days (range, 7–117) and 41 days (range, 17–77), respectively.

Discussion

Cisplatin-based chemoradiotherapy for locally advanced head and neck cancers is now widely recognised as a standard form of therapy for patients with locally advanced disease, although considerable clinical problems remain to be resolved. This can be a rather toxic form of therapy despite using non-surgical modalities [6]. Swallowing dysfunction caused by the therapy sometimes becomes severe, and this is one of the largest obstacles in conducting concomitant chemoradiotherapy for head and neck cancers. Few previous studies have addressed this issue [7], but some reports mentioned that more than half of the cases required enteral feeding temporarily [8], and about 20% required long-term enteral feeding [1]. Nguyen et al. reported that aspiration was frequently observed during the course of therapy, sometimes leading to fatal aspiration pneumonia [9,10]. Swallowing dysfunction leads to malnutrition, which causes body weight loss during the course of therapy. This results in not only physical damage for the patients, but also worsening of the clinical outcome [11]. Body weight loss also causes dosimetric problems. The risk of delivering an inadequate radiation dose to the target volume and critical structures may arise if coordinated replanning is not performed during the course of the therapy, especially when using highly conformal methods [12].

As mentioned above, care must be taken regarding swallowing dysfunction during concomitant chemoradiotherapy for head and neck cancers and appropriate measures should be taken to alleviate secondary averse effects, such as aspiration or body weight loss. Nutritional support is a high priority issue in the management of these patients. Enteral feeding is generally the preferred method [13]. However, total parenteral nutrition was usually adopted in our facility. This might be due to preference of the attending physicians who were also in charge of the management of chemoradiotherapy for oesophageal cancers. Another part of the reason might be that healthcare system in our district has not strictly regulated this procedure.

As a measure for enteral feeding, percutaneous endoscopic gastrostomy (PEG) tube placement is one of the most effective interventions. Prophylactic PEG tube placement has been recognised as a beneficial approach for ameliorating the nutritional status of these patients [2]. Although a relatively safe procedure, PEG placement is invasive and this may leads to critical complications [14]. Therefore, it is not reasonable to place a PEG tube in all patients, and a selection index to identify patients requiring prophylactic PEG tube placement is urgently needed [2]. Several studies have addressed risk factors for severe swallowing dysfunction in radiotherapy for head and neck cancers. Manger et al. argued that clinical stage, general condition and history of smoking may be risk factors for severe dysphagia in chemoradiotherapy for head and neck cancers [8]. Poulsen et al. suggested that irradiated volume of the pharyngeal mucosa and musculature are strongly related to the swallowing toxicity in radiotherapy alone for head and neck cancers [15]. Other factors such as primary site or combined modality were also described as risk factors [2], but there is no comprehensive index in the literature. The Total Dysphagia Risk Score (TDRS) proposed by Langendijk et al. is a predictive model for swallowing dysfunction after curative treatment for head and neck cancers [3]. As this model was derived from data regarding late radiation morbidity, it is intended for prediction of late swallowing dysfunction. However, this simple model may also be useful for predicting acute morbidity, as suggested by Langendijk et al. The results of the present study indicated that TDRS is a valid measure for predicting acute swallowing dysfunction in patients with head and neck cancers undergoing definitive chemoradiotherapy. The TDRS was applicable despite the differences in patient characters and method of therapy. Thus, the TDRS may become an international index to predict swallowing dysfunction. Initially, validity of the TDRS for predicting grade 2 or higher acute swallowing dysfunction was set as the endpoint of the present study. This was due to the fact that the TDRS was defined as a measure to predict RTOG grade 2 or higher swallowing dysfunction. However, more than 80% of the morbidity in patients with experienced grade 2 or higher swallowing dysfunction was severe (grade $\geqslant 3$) in the present study. Then, we set validity of the TDRS for predicting severe acute swallowing dysfunction as another endpoint of this study. ROC analysis in our study suggested that severe acute swallowing dysfunction may be similarly predictive. These observations suggest that the TDRS could be a predictive tool for severe swallowing dysfunction. Thus, the TDRS would allow selection of the patients most likely to benefit from prophylactic PEG placement. Our previous study indicated that radiation portal size is a risk factor for severe swallowing dysfunction in chemoradiotherapy for head and neck cancers [16]. Of the five factors included in the TDRS, T-classification, neck irradiation and primary tumour site are related to radiation portal size.

The annual number of the patients included in this study was relatively low (5–6 patients per year). This was the actual number of patients which we treated during this period. In our facility, definitive chemoradiotherapy has been strictly confined to patients with quite good condition. This might lead to scarcity of the number of patients.

It is obvious that radiotherapy plays a major role in the occurrence of swallowing dysfunction. Broader mucous membranes and more anatomical parts important for swallowing would be affected to a greater degree by larger radiation portals, and these would be amplified by chemotherapy. Therefore, improving radiotherapy may allow reduction of this complication. Intensity-modulated radiotherapy (IMRT) has been widely used for head and neck cancers [17]. Using this advanced technique, complications