radiotherapy between the different surveys. Shibamoto et al. [21] suggested the possible use of partial-brain radiation for solitary lesions, but such a policy has yet to spread nationwide. Reducing total as well as whole-brain radiation doses using chemotherapy has not become popular in Japan. The increased use of systemic chemotherapy and, in particular, MTX-based regimens appear to be a worldwide trend, as was also shown in our study.

The prognosis of PCNSL patients has improved recently. Improvement in supportive care may at least in part have contributed to these changes. The 5-year survival was 30.1 and 36.5 % in 1995–2004 and 2005–2009, respectively. However, relapse-free survival rates did not differ between these two periods, suggesting that although second-line treatment at recurrence has prolonged survival, the cure rate has not yet improved. This trend was also true for patients treated with high-dose MTX and radiation; no improvement was seen for the most recent period, suggesting that, in terms of cure, more than half of PCNSLs are resistant to currently available treatment. New treatments are therefore urgently needed.

Many prognostic factors of PCNSL, such as age, PS, and tumor multiplicity, have been reported [8, 11, 17, 19, 22], and the results of the univariate analyses we conducted in our study agree with previously published data. Consequently, we did not present the multivariate analysis data. In the most recent survey, we paid attention to sIL-2R as a prognostic marker and observed that patients with a high sIL-2R level tended to have a poorer prognosis. The prognostic value of sIL-2R has been reported for extracranial lymphoma [23, 24], but, to our knowledge, its role in PCNSL has not been reported. The serum sIL-2R level reflects the total amount of activated T lymphocytes and is correlated with disease activity [25]. It can also be elevated in cancers other than lymphoma, collagen disease, and infection [25, 26]. Since sIL-2R and LDH levels do not necessarily correlate with each other, sIL-2R may be another useful prognostic marker for PCNSL.

Very recently, a few Japanese groups have started to treat PCNSL patients with chemotherapy alone, following the trend set in Western countries. A randomized European study of chemotherapy alone versus chemotherapy + radiation indicated that chemotherapy alone was associated with a decreased progression-free survival, although overall survival was similar, partly due to the use of radiotherapy as a second-line treatment [27]. Since most studies are conducted in phase II settings, the data presented in our study may serve as a basis for studying the treatment and prognosis of PCNSL patients in Japan.

In conclusion, the results of our study reveal that recent trends in PCNSL are increased patient age, better PS, tumor multiplicity, avoidance of extensive tumor resection, more frequent use of high-dose MTX-containing chemotherapy, and improved survival, with no improvement in relapse-free survival. Newer strategies are therefore necessary to further improve the prognosis of PCNSL patients, and the present data may serve as a basis for designing new studies.

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Conflict of interest The authors declare that they have no conflict of interest.

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CLINICAL STUDY

Risk factors for early death after surgery in patients with brain metastases: reevaluation of the indications for and role of surgery

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Abstract Surgical resection remains an important option for the treatment of brain metastases despite recent advancements in radiotherapy and systemic therapy. When selecting surgical candidates, it is important to exclude terminal cases who will receive neither a survival benefit nor an improvement in their quality of life. We reviewed a total of 264 surgical cases of brain metastases and analyzed the clinical characteristics of early death in order to clarify the indication for and the role of surgery. The median survival time (MST) after surgery in all cases was 12.4 months. Early death was defined as death within 6 months, and 23 % (62 cases) of this series were succumbed to this. A decrease in postoperative Karnofsky performance status (KPS) (<70) ($P = 0.041$), lack of systemic therapy after surgery ($P < 0.0001$), and uncontrolled extracranial malignancies ($P = 0.0022$) were significantly related to early death in multivariate analysis, while preoperative KPS (<70) and recursive partitioning analysis (RPA) class were related to early death only in univariate analysis ($P < 0.05$). When analyzing patients with uncontrolled extracranial malignancies and those with a postoperative KPS score of 70 or greater (who were generally candidates for systemic therapy), the MST was significantly longer in the systemic therapy (+) group compared with the systemic therapy (−) group (12.5 vs. 5.6 months; $P = 0.0026$). Our data indicate that the postoperative RPA class and treatment strategy were associated with early death. Deterioration of patients by surgery should be avoided in the treatment of brain metastases.

Keywords Brain metastases · Surgery · Early death · Leptomeningeal metastases

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Introduction

Brain metastasis is a life-threatening event for cancer patients and indicates that cancer has reached the advanced stages. Surgical resection remains an important option for treatment despite recent advancements in radiotherapy and chemotherapy. The aims of surgical resection are mass reduction and rapid improvement of neurological status.

Knowledge regarding the prognosis of extracranial lesions is important when making decisions about surgery. Several studies have attempted to identify prognostic factors, and various classification systems including recursive partitioning analysis (RPA) classification and graded prognostic assessment (GPA) have been developed [1, 2]. These classification systems have mainly been validated in patient populations treated with radiotherapy; however, some reports have indicated that these systems are useful for predicting survival time after surgery [3–9]. Considering the risks associated with treatment, terminal cases who receive neither a survival benefit nor an improvement in their quality of life (QOL) should be excluded during the selection of surgical candidates.

Herein, we describe a retrospective analysis of the relationship between clinical characteristics and the

outcome of surgery for brain metastases, and we discuss the indications for and the role of surgery.

Materials and methods

Patients

In total, we included 264 cases (156 men and 108 women) who underwent resection as their first surgery for brain metastases at the National Cancer Center Hospital in Japan between January 2000 and December 2011. The mean age of the included patients was 57.5 years (range 19–87), and their clinical characteristics were extracted from their medical records. Overall survival was calculated from the first resection surgery to death. The Karnofsky performance status (KPS) was determined as recorded or was retrospectively estimated from information obtained from the clinical chart by three neurosurgeons (Y.N., Y.M., and S.S.) who performed surgery on the patients. RPA classification of each patient was performed using published criteria [1]. Preoperative status, including performance status and RPA, was evaluated at the time of surgery, while postoperative status was evaluated approximately 1 month after surgery. The performance status and RPA class of patients who died within 1 month after surgery were recorded as 0 and III, respectively. Information regarding the RPA class and status of extracranial malignancy was not available for 1 case.

The cause of death was determined by clinical evaluation. Neurological deaths were defined as cases with neurological deterioration and stable extracranial disease as well as cases with apparent fatal progression of intracranial lesions or leptomeningeal metastases (LMM) regardless of systemic conditions.

The analysis in this study was approved by the local institutional review board (reference no. NCC16-066).

Treatment

Our basic surgical indications for brain metastases were described in a previous report [10]. Surgical candidates included patients with the following characteristics: (1) a post-surgery life expectancy of 6 months or more based on information from medical oncologists, (2) no clinical symptoms or apparent radiological findings indicating LMM, and (3) single metastases measuring $\geqq 3$ cm, or multiple or smaller tumors associated with severe neurological symptoms such as cerebellar metastases. In principle, adjuvant radiotherapy usually began 8 days after surgery. Adjuvant stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) was undergone only for the treatment of the surgical remnant or unresected lesion(s) in patients with multiple metastases. After brain metastases were controlled, patients received further systemic therapy or best supportive care (BSC) according to decisions made by medical oncologists.

A total of 37 patients received RT prior to surgery. In patients who experienced tumor recurrence after radiotherapy, surgical indication was judged via discussion with senior radiologists.

Early death

Early death was defined as death within 6 months after the first surgery for brain metastases, and the clinical profiles between the early death group and the non-early death group were compared. This definition is based on a comparison between the outcome of whole brain radiation therapy (WBRT) and surgery. The median survival time (MST) after WBRT alone is approximately 6 months [11–13]; therefore, if surgery confers a survival benefit, it should extend this time period.

Statistical analysis

Statistical analysis was performed using JMP version 10 (SAS Institute, Cary, NC, USA). The data for survival time were analyzed using the Kaplan–Meier method. A P value below 0.05 was considered statistically significant.

Results

Analysis for all cases

When all cases were analyzed, the median follow-up, MST, 1-year overall survival rate, and 5-year overall survival rate were 11.2, 12.4 months, 52, and 12 %, respectively. The 3 and 6-month overall survival rates were 89 and 75 %, respectively. When patients were divided according to preoperative RPA class, we determined that MST was 21.8 months for class I (59 cases, 22 %), 12.4 months for class II (148 cases, 56 %), and 6.5 months for class III (56 cases, 21 %) (Fig. 1a). When we reevaluated the data using postoperative RPA classification, MST was 20.8 months for class I (66 cases, 25 %), 11.2 months for class II (176 cases, 67 %), and 4.3 months for class III (21 cases, 8 %) (Fig. 1b). Both of pre- and postoperative RPA class were significantly related with survival ($P < 0.0001$, log-rank test). The relationships between preoperative and postoperative RPA class are shown in Supplementary Table 1.

KPS improved in 53 %, was unchanged in 40 %, and worsened in 7 % of all cases after surgery. Surgical complications were observed in 20 cases (7.6 %) including 8 instances of neurological deterioration due to surgical

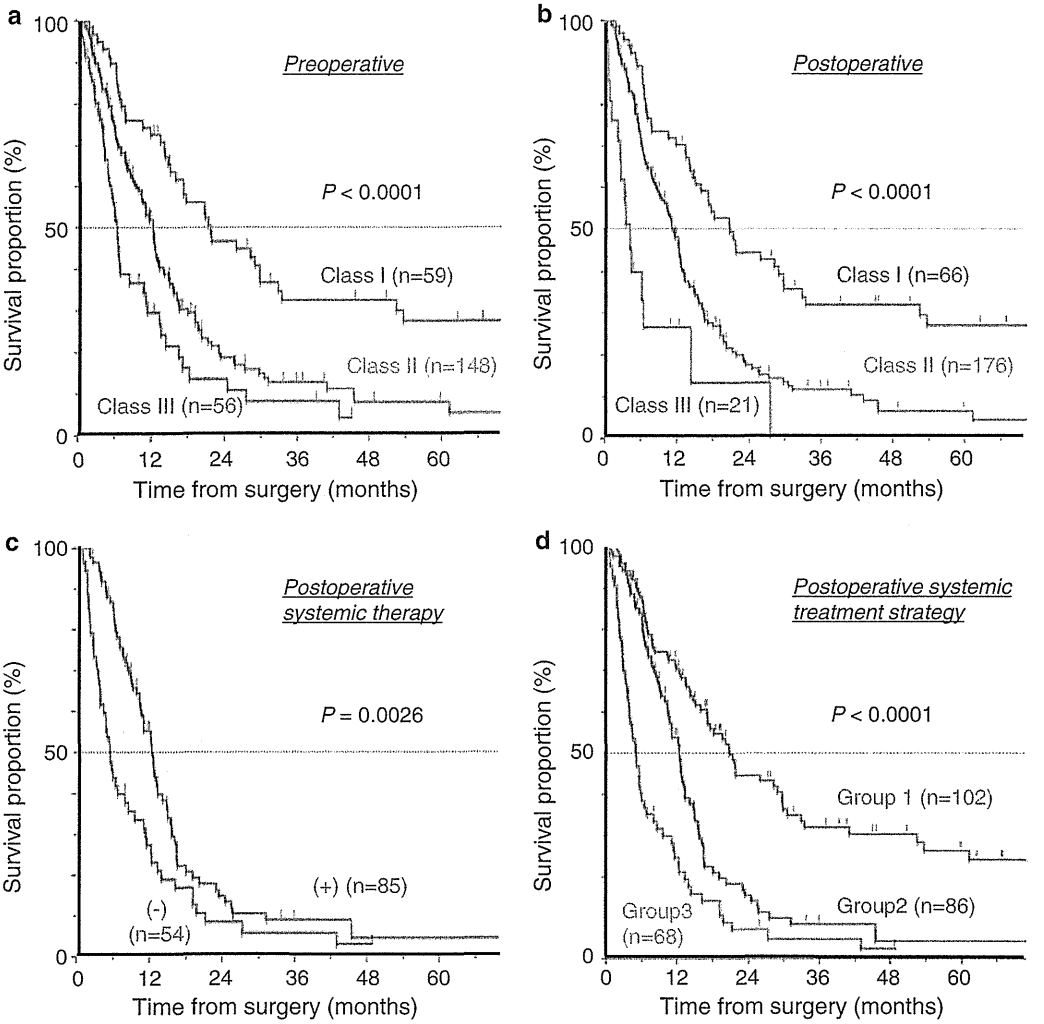

Fig. 1 Survival analysis. **a** Survival curves according to preoperative RPA class. MST was 21.8 months for class I, 12.4 months for class II, and 6.5 months for class III. **b** Survival curves according to postoperative RPA class. MST was 20.8 months for class I, 11.2 months for class II, and 4.3 months for class III. **c** Survival curves according to type of adjuvant therapy in patients with high KPS (70 or more) and uncontrolled extracranial malignancies. MST was 12.5 months for the systemic therapy (+) group and 5.6 months for the systemic therapy (−) group. **d** Survival curves according to postoperative systemic therapy. Group 1 consisted of patients without systemic disease, group 2 consisted of patients undergoing systemic therapy for uncontrolled extracranial disease, and group 3 consisted of patients who had extracranial disease but did not receive systemic therapy. MST was 20.8 months for group 1, 12.4 months for group 2, and 5.1 months for group 3

manipulation, 3 cerebral infarctions, 2 cases requiring evacuation of intraparenchymal hemorrhage, 1 case requiring evacuation of epidural hematoma, 1 case treated conservatively for intraparenchymal hemorrhage, 1 case requiring ventricular drainage for obstructive hydrocephalus, 1 instance of pulmonary embolism, 1 instance of surgical site infection, 1 sudden cardiopulmonary arrest, and 1 instance of vocal paralysis related to intubation. A permanent neurological deficit occurred in 11 (4.2 %) patients, but did not lead to early death in any case. Four patients (1.5 %) succumbed to surgery-related death (i.e., death within 30 days after surgery). Of these, two died of advanced systemic diseases 22 and 30 days after surgery, respectively. The other patients experienced neurological death: 1 died of LMM 23 days after surgery, while the other died of brainstem infarction 17 days after surgery for frontal lobe metastases.

Clinical characteristics of the early death group

A total of 62 patients (23 %) were included in the early death group. The early death rates were 10, 22, and 41 % in preoperative RPA class I, II, and III patients. When patients were divided according to postoperative RPA class, the

Table 1 Patient characteristics

	Total	Early death	Non-early death	*P* value[a]
Patients no.	264	62	202	
Multiple BM	67	24	43	0.0058
Infra-tentorial lesions	79	18	61	0.86
Age 65 or more	82	16	66	0.31
Preoperative KPS <70	57	24	33	0.0002
Postoperative KPS <70	22	13	9	<0.0001
ECM and/or uncontrolled primary lesion[b]	161	50	111	0.0003
Preoperative RPA[b]				0.0059[c]
I	59	6	53	
II	148	33	115	
III	56	23	33	
Postoperative RPA[b]				0.0041[c]
I	66	7	59	
II	176	43	133	
III	21	12	9	
Primary cancer				
Lung	102	24	78	
Breast	48	11	37	
GI	46	14	32	
Malignant melanoma	13	5	8	
Renal	8	2	6	
Others	47	6	41	
GTR	232	53	179	0.51
Any RT prior to surgery	37	11	26	0.33
Adjuvant RT(+)	216	46	170	0.075
Systemic therapy after operation for BM				
(+)	119	16	103	<0.0001
(−)	129	46	83	

BM brain metastases, *ECM* extra-cranial metastases, *GI* gastrointestinal, *GTR* gross total removal, *KPS* Karnofsky performance status, *RPA* recursive partitioning analysis, *RT* radiation therapy, *WBRT* whole brain radiation therapy

[a] Pearson's Chi square test

[b] Data of one case was absent

[c] Analyzing with dividing into RPA I and II-III

early death rates were 11, 24, and 57 % in class I, II, and III patients, respectively.

Table 1 shows the results of univariate analysis of data from the early death group and the non-early death group. The early death group contained a significantly higher ratio of patients with multiple brain metastases, KPS <70, uncontrolled primary cancers, and advanced RPA (II or III). The distribution of primary cancers did not differ significantly between these 2 groups. Fewer patients received systemic therapy after the resection of brain metastases in the early death group than in the non-early death group (26 vs. 55 %).

Table 2 Multiple logistic regression analysis for early death

	Odds ratio	*P* value
Postoperative systemic therapy (−)	4.91	<0.0001
Uncontrolled extra-cranial malignancy (+)	5.22	0.0022
Postoperative poorer KPS (<70)	3.61	0.041
Multiple brain metastases	(2.04)	0.051
Preoperative poorer KPS (<70)	(1.84)	0.18
Preoperative advanced RPA (class II or III)	(0.79)	0.84
Postoperative advanced RPA (class II or III)	(0.96)	0.98
Adjuvant radiotherapy (not performed)	(1.69)	0.21

KPS Karnofsky performance status, *RPA* recursive partitioning analysis

Multivariate logistic regression analysis was performed to identify which factors were most closely related with early death. Only clinical factors with $P < 0.1$ in univariate analysis (as described above) were used for this analysis. As shown in Table 2, uncontrolled primary tumors or extracranial metastases, lack of postoperative systemic therapy, and a postoperative decrease in KPS (<70) were significantly related to early death.

The impact of postoperative systemic therapy on the survival of patients with uncontrolled extracranial disease

The impact of treatment strategy on survival was further analyzed because postoperative systemic therapy was significantly related with early death in the univariate and multivariate analyses described above. Survival analysis using the Kaplan–Meier method did not reveal a difference in survival between patients in the systemic therapy (+) group (119 cases) and the (−) group (129 cases) (12.9 vs. 10.7 months; $P = 0.68$, log-rank test). Because systemic therapy is not usually administered to patients with poor performance status or without extra-cranial malignancies, we performed a further analysis including only patients with uncontrolled extracranial malignancies and those with a postoperative KPS of 70 or more. Based on this analysis, the MST was significantly longer in the systemic therapy (+) group (85 cases) than in the systemic therapy (−) group (54 cases) (12.5 vs. 5.6 months; $P = 0.0026$, log-rank test) (Fig. 1c).

The impact of postoperative treatment strategy on survival

All patients were divided into 3 groups according to treatment course after surgery for brain metastases: group 1

(102 cases) included patients without systemic disease, group 2 (89 cases) included patients who underwent systemic therapy for uncontrolled extracranial disease, and group 3 (65 cases) included patients who had extracranial disease but did not receive systemic therapy. Group 3 patients were treated with best supportive care. The MSTs of groups 1, 2, and 3 were 20.8, 12.4, and 5.1 months, respectively, and the difference among the groups was significant ($P < 0.0001$, log-rank test) (Fig. 1d). The early death rate was 12 % in group 1, 16 % in group 2 and 55 % in group 3, and the early death rate of group 3 was significantly higher than that of the other groups ($P < 0.0001$, Pearson's Chi square test).

Cause of death

Data regarding cause of death was available for 55 of the early death cases. Twenty patients (32 %) died from neurological causes, while 35 patients (56 %) died from systemic diseases. Thirteen of the neurological deaths were attributed to LMM. The adjuvant radiation therapies used in LMM cases were WBRT in 5 and local brain radiation therapy in 3 cases. Five cases did not receive either therapy. Other neurological deaths were due to progression of brain metastases after RT (6 cases) and brain stem infarction (1 case).

Postoperative status and survival time in preoperative RPA class III patients

Patients assessed as preoperative RPA class III ($n = 56$) typically have shorter survival times; therefore, the clinical courses of these patients were further analyzed in order to evaluate the potential treatment benefit. Of these patients, 8 (14 %), 31 (55 %), and 17 (30 %) were postoperative RPA class I, II, and III, respectively. When patients were divided according to postoperative RPA class, MST was 13.6, 6.5, and 3.6 months in class I, II, and III patients, respectively. MST was significantly longer in patients who experienced an improvement in postoperative RPA class ($n = 39$) compared with patients who remained in class III ($n = 17$) (6.9 vs. 3.6 months; $P = 0.019$, log-rank test). KPS was improved in 43 (77 %), unchanged in 10 (18 %), and worsened in 3 (5.4 %) preoperative RPA class III cases after surgery.

We further analyzed the cases showing RPA class III preoperatively but better RPA class postoperatively (I, 8 cases; II 31 cases) in order to discuss the operative indication for preoperative RPA class III patients (Supplementary Table 1). Twelve cases (31 %) of this cohort (39 cases) succumbed to early death after surgery, and their postoperative RPA class was I in one and II in 11. The causes of their early death were mainly consisted of systemic death; systemic disease in 8 cases, leptomeningeal metastasis in 2 cases and unknown in 2 cases. To identify what factor contributed to the early death in this cohort (39 cases), the postoperative treatment strategy was compared between the early death cases (12 cases) and the non-early death cases (27 cases). Eight of the 12 early death cases received best supportive care while 7 of the 25 non-early death cases (2 cases lacked the data) did. Thus, lack of postoperative systemic therapy was also statistically related with the early death in this cohort despite improvement in RPA class (8/12 vs. 7/25; $P = 0.025$, Pearson's Chi square test).

Discussion

In this study, we reviewed a surgical series from a single center and focused on the clinical characteristics of cases with poorer prognosis. Comparing with the recent studies presenting their surgical outcome, our series showed the comparable survival time [3, 6, 7, 9] according to RPA class and the comparable complication rate (7.6 vs. 4.5–14 %) despite the high ratio of RPA class III (21 vs. 5.7–6.8 %) [6, 14, 15]. We showed that postoperative treatment strategy and performance status were the significant factors for early death in multivariate analysis.

Systemic therapy after surgery was previously reported as being significantly related to survival time, but this was contradicted by the result in multivariate analysis [6]. This result simply seems to reflect the bias of the analysis: systemic therapy is usually avoided in patients with poorer performance status or patients without uncontrolled extracranial malignancy. We further analyzed only patients with favorable postoperative KPS scores and uncontrolled extracranial malignancies to ensure that we were only analyzing patients who truly needed further treatment for primary cancer. We showed that postoperative systemic therapy had a significant effect on survival in this population (Fig. 1c). Similarly, multivariate analysis showed that a lack of postoperative systemic therapy was a significant factor for early death, which was mainly analyzed in this study (Table 2). Thus, the treatment strategy for extracranial malignancies should be considered when determining operative indication, and this is supported by the results described in Fig. 1d. In other words, patients who cannot undergo chemotherapy (e.g., due to multidrug resistance to systemic therapy) are at high risk of early death after surgery. We also subjected our cohort to further analysis for survival by dividing three groups time according to the operative period (2000–2003, 2004–2007 and 2008–2011), but the difference in OS or early death rate was not apparent (data not shown). Despite the recent advances in systemic therapeutic agents, brain metastases

Table 3 Review of previous clinical studies: cause of death

Treatment		Pt no.	MST (months)	Neurological death (%)[c]	Systemic death[c]	Unknown[c]
Hashimoto et al. [17]	Surgery + WBRT	66	11.5	37	35 %	31 %
	Surgery + LBRT	64	9.7	36	36 %	29 %
Muacevic et al.[a] [18]	Surgery + WBRT	33	9.5	29	53 %	N.A.
	SRS	31	10.3	11	53 %	N.A.
Aoyama et al. [19]	WBRT + SRS	65	7.5	19	N.A.	N.A.
	SRS alone	67	8.0	23	N.A.	N.A.
Manon et al. [20]	SRS	31	8.3	19	30 %	16 %
Serizawa et al. [21]	SRS	521	9.0	18	N.A.	N.A.
Jawahar et al. [22]	SRS	44	7.0	25	36 %	39 %
Andrews et al. [11]	WBRT + SRS	137	6.5	28	62 %	9 %
	WBRT alone	149	5.7	31	64 %	5 %
Petrovich et al. [23]	SRS for MM	231	8	42	50 %	8 %
	SRS for others	227	6–17[b]	23	70 %	7 %
Agboola et al. [5]	Surgery + RT	125	9.5	25	37 %	6 %
Mintz et al. [13]	Surgery + WBRT	41	5.6	15	46 %	5 %
	WBRT	43	6.3	28	35 %	0 %
Wronski et al. [24]	Surgery ± WBRT	231	13	39	30 %	12 %
Bindal et al. [25]	Surgery ± WBRT	82				
	Multiple lesions	56	10	36	32 %	23 %
	Single lesion	30	14	25	45 %	15 %
Vecht et al. [16]	Surgery + WBRT	32	10	32	N.A.	N.A.
	WBRT	31	6	33	N.A.	N.A.

LBRT local brain radiation therapy, *MM* malignant melanoma, *MST* median survival time, *RT* radiation therapy, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiation therapy

[a] The ratio was evaluated with 1-year rate

[b] The ratio was described in each cancer

[c] Deaths of combined cause of systemic and neurological were not included in any groups. When unknown cause were excluded from analysis in the original articles, the ratios were re-estimated including deaths of unknown causes

may arise after acquiring drug resistance even for newly developed agents, and the survival after brain metastases might depend largely on whether further systemic therapy can be available or not.

One of the challenges in our study was evaluating both preoperative and postoperative status. The prognostic significance of pre- and postoperative RPA class was previously analyzed, and the multivariate analysis showed that only preoperative RPA was significant [9]. This observation was, however, based simply on the analysis of survival time. Our analysis differed from the previous study because we evaluated the factor related to early death and specifically analyzed the group with the poorest prognosis: preoperative RPA class III patients. In the present study, postoperative RPA class was related to survival and a higher early death rate, and the early death rate was extremely high in preoperative RPA class III patients without postoperative improvement. Because RPA class III simply indicates a poor KPS score (<70), improvement in performance status is a significant factor for survival in preoperative RPA class III patients. Therefore, when determining the indications for surgery in preoperative RPA class III patients, it is important to consider whether surgery is likely to improve KPS. Patients who are not likely to experience an improvement in performance status are also not likely to obtain a survival benefit. However, it is important to remember that the postoperative treatment strategy is also significant factor for survival as shown in our analysis for RPA class III patients.

Finally, we analyzed the cause of death. Previous studies have reported a neurological death rate of 15–37 % after surgery for brain metastases [5, 11, 13, 16–25] (Table 3). Our results were in line with this, although one limitation of our study was that the cause of death was available only for early death cases. Of note, 21 % (13/62) of early death cases were attributed to LMM in this study. Recent large studies reported a 5–16 % incidence of LMM after surgical removal [14, 17, 26, 27]. Considering these results, LMM

appears to occur early after surgery and may be a significant cause of early death. An increased incidence of early death might be attributed to either (1) preoperative undiagnosed LMM without apparent radiological findings because of a lack of routine cerebrospinal fluid cytology [26] or (2) LMM caused by the surgery itself. In fact, several previous reports have shown an increased risk of LMM after surgery compared with SRS alone [14, 26–28]. In order to reduce early deaths due to LMM, adjuvant therapies will need to be developed. The protective effect of adjuvant radiation therapy for LMM remains controversial, and recent studies have failed to demonstrate this effect [14, 26]. Further studies are needed to clarify the efficacy of radiation therapy.

In summary, early death after resection of brain metastases can be attributed to neurologic factors and systemic factors. Of the neurological factors, LMM is a critical factor that is related to early death. Further studies exploring the prevention and treatment of LMM are necessary. Of the systemic factors, a poor performance status after surgery (rather than before surgery), uncontrolled extracranial malignancies, and a lack of systemic therapy after surgery are related to early death. The limitation of our retrospective study lies in the possibility of the bias derived from patient selection. Further analysis including non-surgically treated cases may confirm our observations. When making decisions regarding surgery for brain metastases, physicians should be aware of the importance of a systemic treatment strategy after surgery, while surgeons should recognize that a poor performance status deprives patients of QOL and a chance for systemic therapy. The role of surgery for brain metastases is not only to improve the QOL and prevent neurological death but also to give patients a chance for further systemic therapy.

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Conflict of interest The authors declare that they have no conflict of interest.

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Clinical Efficacy of Alternating Chemoradiotherapy by Conformal Radiotherapy Combined with Intracavitary Brachytherapy for High-risk Cervical Cancer

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Objective: The purpose of this study was to assess the outcome of alternating chemoradiotherapy in patients with high-risk cervical cancer.
Methods: We performed definitive alternating chemoradiotherapy in cervical cancer patients with at least one high-risk factor such as International Federation of Gynecology and Obstetrics III or IVA disease, primary tumor diameter ≥50 mm, positive pelvic node, and positive para-aortic node. Our chemoradiotherapy protocol was as follows: (i) alternating chemoradiotherapy with 5-fluorouracil and nedaplatin; (ii) whole pelvic radiotherapy with the dynamic conformal technique combined with intracavitary brachytherapy; (iii) prophylactic irradiation to the para-aortic region for International Federation of Gynecology and Obstetrics III/IVA or positive pelvic node and full-dose radiotherapy for positive para-aortic node. Between 1998 and 2010, 121 patients were treated with this protocol.
Results: The median follow-up period was 53.7 months (7.6–162.2). International Federation of Gynecology and Obstetrics stages were IB; (9.1%), IIA; 6 (5.0%), IIB; 53 (43.8%), IIIA; 7 (5.8%), IIIB; 37 (30.6%) and IVA; 7 (5.8%), respectively. Nodal involvement was reported in 77 patients (63.6%) at the pelvis and 25 (20.7%) at the para-aortic region. The 5-year overall survival and progression-free survival rates were 80.0 and 63.4%, respectively. Regarding Grade ≥3 late toxicities, three patients developed urinary and three developed intestinal toxicities. We encountered no treatment-related death.
Conclusions: The clinical results of our alternating chemoradiotherapy protocol for high-risk cervical cancer are promising.

Key words: gynecol-radoncol – radiation oncology – chemo-gynecology

INTRODUCTION

The efficacy of chemoradiotherapy for cervical cancer has been previously reported. Five randomized trials since 1999 have demonstrated the efficacy of concurrent chemoradiotherapy over to radiotherapy alone (1–5), and the results were also confirmed with meta-analyses for both survival and disease control (6,7). A cisplatin-based regimen has been considered as a standard treatment for cervical cancer. In the GOG 120 trial, the incidence of acute toxicities in the cisplatin and 5-fluorouracil (5-FU) arm was higher than that in the weekly cisplatin arm. Therefore, weekly cisplatin has been recognized as the standard treatment with a reduced risk of acute toxicities. However, the dose of cisplatin used in this regimen is thought to be insufficient to control distant metastasis, which

is why an apparent survival improvement in overall survival was not reported in the Stage III/IV subgroup with longer follow-up data in the RTOG 90-01 trial (8). In Japan, the majority of cervical cancer patients who undergo chemoradiotherapy have more advanced disease than that in patients in North America and European countries, therefore distant failure is an important issue in clinical practice (9).

In our institution, we treated high-risk cervical cancer patients with alternating chemoradiotherapy using nedaplatin and 5-FU. The clinical advantage of nedaplatin is that it is associated with lower incidence of renal and gastrointestinal toxicities than that of cisplatin. Furthermore, alternating chemoradiotherapy allows the patients to receive a sufficient dose of drugs while avoiding acute toxicities by concurrent administration, which could lead to a decrease in distant metastasis. A Phase I/II trial of alternating chemoradiotherapy was previously conducted in our institution (10). In this analysis, we retrospectively evaluated the efficacy and feasibility of our protocol in patients with high-risk cervical cancer.

PATIENTS AND METHODS

Patients

Between 1998 and 2010, 130 patients with cervical cancer with at least one high-risk factor such as International Federation of Gynecology and Obstetrics (FIGO) III/IVA, primary tumor diameter $\geq$50 mm, positive pelvic node (PN), and positive para-aortic node (PAN) underwent definitive alternating chemoradiotherapy. In this study, we excluded one patient with adenocarcinoma, three with adenosquamous carcinoma, and five patients who were irradiated to the pelvis at a dose $<$40 Gy, because we considered that at least 40 Gy was necessary to radically cure the illness. We analyzed a total of 121 patients.

Evaluation

Prior to the treatment protocol, each patient underwent physical, laboratory and radiological examinations. Laboratory examinations included a complete blood cell count, measurement of liver and renal functions and electrocardiography. Computed tomography (CT) and magnetic resonance imaging (MRI) were used to evaluate the pelvis and abdomen. CT of the neck and lungs was also taken for screening of distant metastasis. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) was also performed if possible from 2004. Positive nodal involvement was defined as a nodal size $>$10 mm in minimal diameter on CT or MRI as the criteria used in our previous study (11). If positive findings in FDG-PET, these were also defined as lymp node (LN) involvement. Clinical stages were decided according to the classification of the FIGO.

Treatment

Radiotherapy

The treatment scheme is shown in Fig. 1. Details of the treatment regimen and radiation technique have been reported previously (10). Radiotherapy using a 10 MV photon beam from a linear accelerator was initiated 1 day after the end of systemic chemotherapy. Whole pelvic irradiation was performed daily at a dose of 1.9–45.6 Gy in 24 fractions using two-axial dynamic conformational techniques. In the case of a bulky primary tumor without sufficient dose coverage for the target volume, we initially used the four-field technique and then switched to dynamic conformal irradiation if the primary tumor responded. We prescribed 51.3 Gy to the whole pelvis of patients with positive PN followed by an additional boost to a maximum of to the involved LN.

Prophylactic radiotherapy to the para-aortic region for FIGO III/IV or positive PN was given at 36 Gy in 20 fractions until 2007. After 2008, Prophylactic irradiation to the para-aortic region was omitted if negative PAN was observed with FDG-PET. Prophylactic para-aortic irradiation was not adapted to patients with FIGO I/II disease without PN involvement. Patients with positive PAN received 36 Gy to the para-aortic region, followed by an additional boost of 14 Gy to the positive node.

MRI was performed at a dose of ~30 Gy to confirm that the primary tumor had been reduced to the range covered by the sufficiently high-dose area of intracavitary brachytherapy (ICBT). ICBT was then performed during the external beam radiation therapy (EBRT) procedure. However, both pelvic EBRT and ICBT were not treated in the same day. Before March 2002, 24 Gy in two fractions to Manchester point A were given in low-dose-rate (LDR) brachytherapy with Radium-226 (Ra-226). After that, we prescribed 15–20 Gy in 3–4 fractions to point A using high-dose-rate (HDR) brachytherapy with Iridium-192 (Ir-192).

Chemotherapy

The treatment scheme is shown in Fig. 1. Details of the treatment regimen have been described in a previous report (10). Briefly, patients received chemotherapy with 5-FU and nedaplatin. 5-FU was administered continuously at a dose of 700 mg/m^2 on Days 1–5 and nedaplatin at a dose of 120–140 mg/m^2 on Day 6. Between 1998 and 2008, nedaplatin was administered at a dose of 140 mg/m^2, with the dosage being reduced to 120 mg/m^2 from 2009 to reduce hematological toxicity. We performed three cycles of this regimen once a month. Chemotherapy and radiotherapy were performed alternatingly.

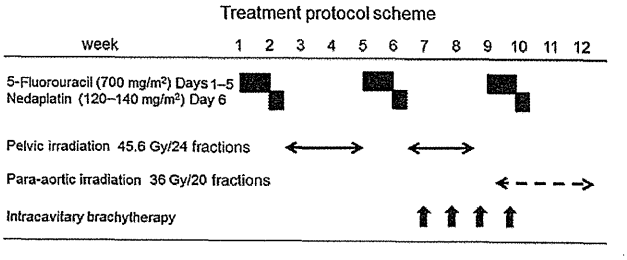

Figure 1. Treatment protocol scheme. 5-FU, 5-fluorouracil; RT, radiotherapy.

Statistical Analysis

Overall survival (OS) was calculated from the date of the first day of chemotherapy to the date of death from any cause or of the last follow-up alive. Progression-free survival (PFS)/loco-regional progression-free survival (LRPFS)/distant metastasis-free survival (DMFS) were defined as the period from the date of the first day of chemotherapy to the date of first recurrence at any site/first recurrence of the primary site or PN/any distant metastasis including PAN recurrence or death or the date of the last follow-up. Survival estimates were calculated using the Kaplan–Meier method. The log-rank test was used to compare the survival curves of two groups. Multivariate analysis was performed with the Cox proportional hazard model.

Acute toxicities were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (12). The grading of late toxicities was in accordance with the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) toxicity criteria. CTCAE version 3.0 was used for bone fractures. Differences in ratios between the two groups were compared using Fisher's exact test.

RESULTS

Patient Characteristics

Table 1 summarizes patient and tumor characteristics. The median age of patients was 56 years old (range; 31–78). FIGO stages were IB; 11 (9.1%), IIA; 6 (5.0%), IIB; 53 (43.8%), IIIA; 7 (5.8%), IIIB; 37 (30.6%) and IVA; 7 (5.8%), respectively. Seventy-seven patients (63.6%) were revealed as positive PN, while 25 (20.7%) were positive PAN, respectively. The median tumor diameter of the primary tumor measured by MRI images was 58 mm (range; 28–100 mm).

Radiation Treatment and Chemotherapy

The median dose of the whole pelvis was 51.8 Gy (range; 40–70.2 Gy), and positive PN received 57.3 Gy (range; 46.1–64.6 Gy). ICBT was performed in 119 patients with a median point A dose of 24.5 Gy for Ra-226 ($n = 27$; 23%) and 15 Gy for Ir-192 ($n = 92$; 76%), respectively. Two patients did not receive ICBT. One patient refused ICBT, while the other patient could not be inserted for tandem. They received EBRT to the primary region up to a dose of 70.2 and 59.4 Gy, respectively. Sixty-five patients received a nedaplatin dose >130 mg/m^2, while 56 received <130 mg/m^2. The cycles of chemotherapy administered were one; 16 (13.2%), two; 46 (38.9%), and three; 59 (48.8%). Eighteen patients required dose reduction of nedaplatin or 5-FU in the second cycle of chemotherapy. At the second cycle, chemotherapy was postponed within 1 week in 33 patients, while >1 week in 54 patients. The main reasons of dose reduction or prolongation of chemotherapy were acute hematologic and gastrointestinal toxicities.

Table 1. Patient characteristics

Age	56 (31–78)
International Federation of Gynecology and Obstetrics (FIGO) stage	
IB	10 (9.1%)
IIA	6 (5.0%)
IIB	54 (44.6%)
IIIA	7 (5.8%)
IIIB	37 (30.6%)
IVA	7 (5.8%)
PN	
Negative	44 (36.3%)
Positive	77 (63.6%)
PAN	
Negative	96 (79.3%)
Positive	25 (20.7%)
Maximum tumor diameter (mm)	58 (22–100)

PN, pelvic node; PAN, para-aortic node.

The median overall treatment time of radiation with or without para-aortic irradiation was 56 days (range; 36–94) or 82.5 days (range; 50–120). The median overall treatment time of the whole regimen including both radiotherapy and chemotherapy was 85 days (range; 44–132).

Survival

The median follow-up time was 53.7 months (range; 7.6–162.2) for all patients and 55.7 months (range; 7.6–162.2) for surviving patients. Eighty patients were alive without evidence of disease and 17 patients were alive with disease at the last follow-up. Twenty-one patients died of cervical cancer, two patients died of other diseases, and one patient died of an unknown cause. The 5-year OS and PFS rates were 80.0% (95% confidence interval [CI], 72.2–87.8%) and 63.4% (95% CI, 54.2–72.6%), respectively (Fig. 2A).

No significant differences were observed in 5-year OS rate, FIGO stage, positive PN, positive PAN, tumor size, dose of nedaplatin, and source of ICBT between the two groups. A significant unfavorable factor for PFS was shown to be positive PN. A significant correlation was not reported for FIGO stage, positive PAN, tumor size or dose of nedaplatin with PFS. We examined the aforementioned variables using multivariate analysis. Positive PN was also revealed as significantly unfavorable factor of PFS ($P = 0.02$). We could not find any significant prognostic factor of OS with multivariate analysis (Table 2).

Para-aortic Irradiation

Ninety-six of 121 patients were revealed to be negative PAN in our cohort. Twenty-six of the 96 patients were FIGO I/II, bulky primary tumor, and N0 stage, and 70 patients were

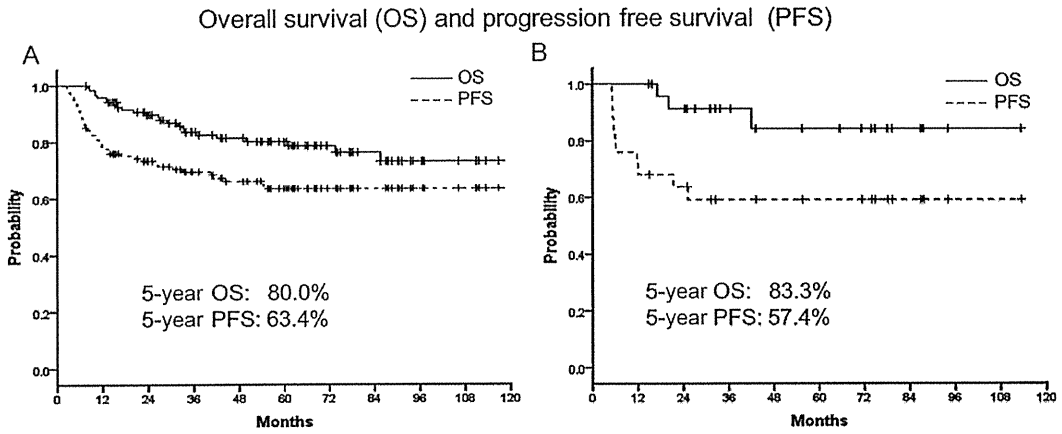

Figure 2. Survival curves of overall and progression-free survival. A: Survival for all 121 patients. B: Survival for 25 patients with positive para-aortic node.

Table 2. Univariate and multivariate analyses regarding OS and PFS

	Number	Univariate analysis		Multivariate analysis			
		OS	PFS	OS		PFS	
		P value	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
FIGO stage							
I–II	70	0.48	0.56	0.71 (0.29–1.75)	0.46	1.22 (0.60–2.49)	0.58
III–IV	51						
PN							
Negative	44	0.30	0.01	0.52 (0.21–1.28)	0.15	0.37 (0.17–0.80)	0.02
Positive	77						
PA							
Negative	96	0.34	0.39	3.05 (0.68–13.74)	0.15	1.23 (0.51–2.95)	0.64
Positive	25						
Tumor diameter							
<50 mm	31	0.33	0.64	0.84 (0.46–1.52)	0.55	0.81 (0.54–1.21)	0.30
≥50 mm	84						
Nedaplatin dose							
<130 mg/m^2	56	0.59	0.78	0.97 (0.61–1.54)	0.89	1.13 (0.80–1.59)	0.49
≥130 mg/m^2	65						
ICBT							
Ra	27	0.58	0.68	0.91 (0.37–2.26)	0.84	1.02 (0.47–2.23)	0.96
Ir	92						

OS, overall survival; PFS, progression-free survival; ICBT, intracavitary brachytherapy; HR, hazard ratio; CI, confidence interval.

FIGO III/IV or N1 stage. Of these 70 high-risk cases, 49 patients underwent prophylactic irradiation to the para-aortic region until 2007, while 21 patients were omitted from prophylactic para-aortic irradiation after 2007. We stated the survival rate as a 2-year rate to compare between with and without prophylactic para-aortic irradiation because we omitted prophylactic irradiation from 2008. No significant difference was observed in either the 2-year OS (89.7 vs. 90.5%, $P = 0.61$) or 2-year PFS (73.4 vs. 76.6%, $P = 0.44$) rates between the two groups. Five of 49 patients (10.2%) who

received prophylactic para-aortic irradiation, and two of 21 patients (9.5%) who did not relapsed at the para-aortic region, respectively.

Twenty-five of 121 patients had positive PAN. At the last follow-up, 15 patients were alive without evidence of disease and 7 patients were alive with disease. Two patients died of cervical cancer, and one died of an unknown cause. Ten out of 25 patients having positive PAN developed disease recurrence. One patient underwent simple total hysterectomy and bilateral salpingo-oophorectomy, 8 patients underwent salvage chemotherapy. One patient only underwent best supportive care. Initial salvage chemotherapy regimens were comprised of FN for 2 patients, taxane containing regimen for 5, and others for one patient. The 5-year OS and PFS rates of positive PAN group were 83.3 and 57.4%, respectively (Fig. 2B).

Patterns of Recurrence

The 5-year LRPFS and DMFS rates were 76.6 and 78.2%, respectively. A significant unfavorable factor for 5-year LRPFS was positive PN (93.0 vs. 63.1%, $P = 0.015$). The overall treatment time of pelvic irradiation divided by the cut-off value of 56 days did not show significance as for 5-year LRPFS (85.1 vs. 73.6%, $P = 0.127$). No significant prognostic factor was revealed in the analysis of DMFS.

Fifty-two recurrences out of 41 patients developed in 9 local sites, 20 PN sites and 23 distant sties, respectively. The sites of distant progression were the para-aortic region; 7, mediastinal LN; 6, supraclavicular LN; 6, lung; 10, liver; 1, bone; 4, skin; 1 and brain; 1, respectively.

Toxicities

Of 121 patients, 84 (67.8%) had leucopenia, 34 (28.1%) had thrombocytopenia and 32 (26.4%) had anemia equal to or larger than Grade 3. No significant renal toxicities were reported. Regarding Grade 3 or higher late toxicities (RTOG/EORTC), we encountered 3 (2.5%) urinary and 3 (2.5%) intestinal toxicities, respectively. Acute and late toxicity profiles are shown in Supplementary data, Table.

In the LDR group ($n = 23$), one patient (4.3%) had Grade 2 and two patients (8.7%) had Grade 3 urinary toxicities. In the HDR group ($n = 92$), one patient (1.1%) had Grade 2 and one had Grade 3 urinary toxicities. Gastrointestinal toxicity of Grade 2 or more was not reported in the LDR group. Seven patients (7.6%) had Grade 2 gastrointestinal toxicities and three patients (3.3%) had Grade 3 in the HDR group.

Grade 3 urinary toxicities were observed in two patients (4.1%) with para-aortic prophylactic irradiation and in one patient (4.7%) without para-aortic irradiation. Grade 3 gastrointestinal toxicities were observed in one patient (2%) with para-aortic prophylactic irradiation and in two (9.5%) without para-aortic irradiation. No significant difference was observed between the two groups by Fisher's exact test ($P > 0.05$).

Insufficient bone fractures occurred in four patients (3.3%), all of whom had Grade 2 toxicities in CTCAE version 3.0. Three of four patients underwent para-aortic irradiation (36–54 Gy), while the remaining patient did not. No significant difference was observed between the two groups. We encountered no treatment-related death.

DISCUSSION

We previously reported that both tumor size and PN evaluated by MRI were significant prognostic factors for Stage II disease treated with radiotherapy alone (11). Based on this finding, we developed a distinct strategy for high-risk patients with bulky disease, PN involvement and advanced stage disease. We consecutively adapted our protocol of alternating chemoradiotherapy for these high-risk populations to improve disease control in our institution.

Previous chemoradiotherapy trials treated similar stage patients to the present study (Table 3) (13,14). Although the FIGO stages of the GOG 85 (4), RTOG 90-01 (1) and GOG 120 (2,15) trials were similar to ours, PAN was surgically evaluated, and histologically positive cases were strictly excluded in these trials. Moreover, the rate of PN involvement was lower than ours (12.5–39.1%). Our present study included 24 patients (20.6%) with positive PAN and 77 patients (63.7%) with positive PN; therefore, our cohort appeared to have relatively high-risk patients. Although we need to take into account that we did not histologically evaluate positive LN, we consider the present study to have more promising OS and PFS rates than previously reported series.

One reason for this may be the clinical benefit of alternating chemoradiotherapy. Alternating chemoradiotherapy may reduce acute toxicities to avoid concurrent administration chemotherapy during radiotherapy. The concurrent use of 5-FU with pelvic irradiation has been shown to increase intestinal toxicities, such as diarrhea, which requires the interruption of chemoradiotherapy. Alternating chemoradiotherapy may reduce acute toxicities and improve the completion rate without reducing the intensity of systemic chemotherapy. In our report, 105 patients (86.8%) received two or more cycles, and 59 patients (48.8%) received three cycles of chemotherapy. Thus, we consider dose-intensive chemotherapy to be achievable, which may improve distant tumor control. The 5-year DMFS rate was 78.2% and the distant failure rate was 19% in this study, which is thought to be promising because our cohort comprised a high-risk population. The efficacy of alternating chemoradiotherapy has also been reported in patients with nasopharyngeal cancer, for which large field irradiation and high-dose chemotherapy is thought to be crucial (16).

However, a weak point of alternating chemoradiotherapy is prolongation of the overall treatment time. Generally prolonged treatment period are considered as having a negative impact on the efficacy of definitive radiotherapy for squamous cell carcinoma. In our study, 25 patients (20.6%) developed local failure, which was consistent with reported studies. Patients with OTT <56 days showed a tendency for having higher pelvic control rate; however, it did not reach to

Table 3. Comparison of our results with other studies

Authors	Number	FIGO stage	Percentage (%)				Chemotherapy	5-year OS rate (%)	5-year PFS rate (%)	Late toxicities ≥G3 (%)
			Maximum tumor diameter >50 mm	Stage III /IV	PN+	PAN +				
GOG 85	177	IIB–IVA	77.4	38.9	15.8	0	CDDP + 5-FU	65	60	16.2
RTOG 90-01	195	IIB–IVA	94	30.2	24.1	0	CDDP + 5-FU	73	67	13
GOG 120	176	IIB–IVA	72.1	46.6	12.5	0	weekly CDDP	60	58	2.7
	173	IIB–IVA	71	53.8	12.5	0	CDDP + 5-FU	61	57	0.9
Paker	92	IB1–IVA	NS	29.3	39.1	0	Weekly CDDP	55	57	4
Chung	63	IIB–IVA	71	22.2	71.4	19	Weekly CDDP	77	NS	14
Kodaira	40	IB2–IVA	NS	65	62.5	12.5	CDGP + 5-FU	78.8	66.5	5.0
Our study	121	IB2–IVA	69.4	36.3	63.7	20.6	CDGP + 5-FU	80	63.4	5.0

NS, not stated; RTOG, Radiation Therapy Oncology Group; GOG, Gynecologic Oncology Group; CDDP, cisplatin; 5-FU, 5-fluorouracil; CDGP, nedaplatin.

Table 4. Comparison of the clinical results of definitive chemotherapy obtained in patients with common iliac or para-aortic involvement

Authors	Number	FIGO stage	Chemotherapy	Extended-field irradiation	5-year OS rate (%)	5-year PFS rate (%)	Late toxicities ≥G3 (%)
Varia	86	I–IVA	CDDP + 5-FU	+	39[a]	34[a]	14
RTOG 92-10	33	I–IVA	CDDP + 5-FU	+	29[b]	37[b]	21
Walker	27	IB2–IVA	Weekly CDDP + PTX	+	45	NS	11
Rajasooriyar	39	I–III	Weekly CDDP	+	26	19.4	5.1
Our study	25	IB2–IVA	CDGP + 5-FU	–[c]	80	63.4	5.0

LN, lymph node; PTX, paclitaxel.
[a]Three-year survival.
[b]Four-year survival.
[c]Sequential irradiation.

statistical significance (5-year LRPFS; 85.1 vs. 73.6%, $P = 0.127$). Therefore, we considered that prolonged treatment time did not show critical demerit on local control in our cohort.

The efficacy of prophylactic para-aortic irradiation for advanced cervical cancer patients still remains controversial. We initially performed prophylactic para-aortic irradiation in patients with FIGO III/IV or positive PN. However, we omitted prophylactic irradiation if FDG-PET scans revealed negative PAN in 2008 to acquire accurate diagnostic quality for PAN involvement (17). Because of the relatively shorter follow-up time in the subgroup without prophylactic irradiation, we could not find an apparent increase in para-aortic nodal recurrence until now. Therefore we consider protocol modifications without prophylactic radiation to be acceptable.

Patients with PAN metastasis generally have a poorer prognosis. Extended-field radiotherapy is commonly used; however, the increasing incidence of acute and late toxicities has become a critical issue in patient management. Table 4 shows the results of extended-field irradiation for para-aortic or common iliac LN positive patients (18–21). Grigsby et al. (19) reported the results of the RTOG 92-10 trial, in which accelerated irradiation with extended-filed and concurrent chemotherapy using cisplatin plus 5-FU was evaluated. They reported 24% Grade 3 or more late toxicities in long-term follow-up. Varia et al. (18) also reported that 14% of late toxicities occurred in patients who had undergone extended-field irradiation with concurrent chemotherapy of cisplatin and 5-FU. In our protocol, pelvic and para-aortic regions were sequentially irradiated using alternating chemoradiotherapy; therefore, we believe that our technique represents an adequate method to decrease toxicities without sacrificing treatment efficacy. Although this method prolongs the treatment time, our results appear to be promising because the 5-year OS and PFS rates were 83.3 and 57.4%, respectively, in 25 patients with positive PAN.

Our results of 25 patients with positive PAN proved to be promising compared with reported series (18–21). One of the reasons of successful outcome might belong to the benefit of alternating chemoradiotherapy in possibility of extended-field

radiation therapy with intensive chemotherapy. Moreover, a nedaplatin dose of 120–140 mg/m^2 accompanied with 5-FU administration was considerably intensive dose; therefore, it should lead to reducing distant metastasis.

However, there are several limitations in present study, especially for patients having positive PAN. At first, the follow-up time of this group was slightly shorter (42.1 months) than that of the entire cohort (53.7 months). Secondly, the nodal involvement was only assessed by radiological imaging, not surgical staging, which might led to decrease accuracy of lymph node involvement.

Although serious acute hematological toxicities were observed, such as Grade 3 or higher, with neutropenia being reported in 67.8% patients, thrombocytopenia in 28.1%, and anemia in 26.4%, they were manageable and no treatment-related death occurred. The late toxicities rate was under 5% in our study, which was comparable to other studies (Table 3). Because more than half of our patients were treated with pelvic and para-aortic irradiation, the result acquired was acceptable. Symptomatic bone fractures were observed in the pelvic bone and lumbar spine of four patients. Kathleen analyzed 300 patients who underwent radical or postoperative radiotherapy and reported that ~10% had pelvic bone fractures, and 45% of these were symptomatic (22). Another study reported the frequency of fractures to be 2–10% (23–27). As our study was a retrospective analysis, bias should be considered when we analyze the frequency of fractures.

Kang et al. (28) reported the results of cervical cancer patients who were treated with platinum based chemoradiotherapy, in which positive PN and/or PAN diagnosed by FDG-PET revealed as unfavorable prognostic factor of distant failure. Parker et al. (14) reported PN involvement proved to be prognostic factor of OS in cervical cancer patients treated with cisplatin-based chemoradiotherapy. In present study we could not find apparent correlation between having positive LN and OS, while positive PN proved to be an unfavorable factor of PFS. One of the reasons was that the majority of our cohort consists of patients with high-risk factors with at least one of following criteria; such as disease with FIGO III/IV, primary tumor size $\geq$50 mm, or positive PN or PAN. Positive PN revealed as unfavorable prognostic factor of PFS in present analysis, therefore to refine the clinical outcomes of this group, more intensive treatment warrants to be tested in prospective trial.

Nedaplatin was developed in Japan with the aim of producing a treatment with similar effectiveness to cisplatin, but decreased renal and gastrointestinal toxicities (29). No Grade 3 or more renal toxicities were observed in our cohort, and gastrointestinal toxicities were relatively low, such as nausea: 6.6%, anorexia: 16%, except for moderate to severe diarrhea due to 5-FU. Nedaplatin is also considered to have especially favorable efficacy towards cervical cancer. Radiation therapy combined with nedaplatin and 5-FU for nasopharyngeal and esophageal carcinoma had also favorable clinical results in our institution (16,30). We reported the sufficient efficacy and acceptable toxicities by alternating chemoradiotherapy with nedaplatin and 5-FU in our protocol. However, this result is not supported by sufficient evidence because this study was retrospective and a single-center analysis. The current standard treatment for high-risk cervical cancer is cisplatin-based concurrent chemoradiotherapy. Therefore, further investigations to determine the efficacy and tolerance of alternating chemoradiotherapy using prospective randomized controlled trials are warranted.

CONCLUSION

The clinical outcomes from alternating chemoradiotherapy for high-risk cervical cancer patients, especially with highly advanced nodal disease, regarding both sufficient efficacy and acceptable low toxicity are promising. A prospective multicenter trial is warranted.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

Conflict of interest statement

None declared.

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Clinical Trial Note

Randomized Phase II/III Trial of Post-operative Chemoradiotherapy Comparing 3-Weekly Cisplatin with Weekly Cisplatin in High-risk Patients with Squamous Cell Carcinoma of Head and Neck: Japan Clinical Oncology Group Study (JCOG1008)

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A randomized Phase II/III study was launched in Japan to evaluate the non-inferiority of concurrent chemoradiotherapy with weekly cisplatin (40 mg/m^2) compared with concurrent chemoradiotherapy with 3-weekly cisplatin (100 mg/m^2) for post-operative high-risk patients with locally advanced squamous cell carcinoma of head and neck. This study began in October 2012, and a total of 260 patients will be accrued from 18 institutions within 5 years. The primary endpoint of the Phase II part is proportion of treatment completion and that of the Phase III part is overall survival. The secondary endpoints are relapse-free survival, local relapse-free survival, nutrition-support-free survival, non-hospitalized treatment period during permissible treatment period and adverse events. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009125 [http://www.umin.ac.jp/ctr/].

Key words: head and neck cancer – post-operative chemoradiotherapy – high-risk patients – clinical trials – Phase II/III

INTRODUCTION

Head and neck cancer is relatively rare but increasing steadily in Japan. Squamous cell carcinoma is the most common histological type and comprises ~90% of head and neck cancer.

The prognosis of post-operative Stage III/IV locally advanced squamous cell carcinoma of head and neck (SCCHN) is still poor. Integrated analysis of RTOG95-01 (1) (Radiation Therapy Oncology Group) and EORTC22931 (2) (European Organisation for Research and Treatment of Cancer) demonstrated that microscopically positive resection margin and extracapsular nodal extension are high-risk factors for recurrence in post-operative locally advanced SCCHN. Moreover, these two trials revealed that the standard therapy for post-operative locally advanced SCCHN with high-risk factors for recurrence is surgery followed by chemoradiotherapy (CRT) with 3-weekly cisplatin (CDDP) at 100 mg/m^2 (3-weekly CDDP + RT); this adjuvant 3-weekly CDDP + RT showed 5-year survival of ~50% (1–4).

Meanwhile, concurrent CRT with weekly CDDP at 40 mg/m^2 (weekly CDDP + RT) is a promising regimen for post-operative locally advanced SCCHN with high-risk factors for recurrence. CDDP is expected to have a radiosensitizing effect when it is administered every week during radiation therapy and the dose intensity of weekly CDDP (40 mg/m^2/week) is higher than that of 3-weekly CDDP (33 mg/m^2/week). In fact, promising results of post-operative weekly CDDP + RT were reported in two prospective trials (5,6). In addition, weekly CDDP + RT has several advantages over 3-weekly CDDP + RT in terms of safety and toxicity. First, hematological toxicity tends to be milder in weekly CDDP + RT than in 3-weekly CDDP + RT. In particular, most published reports described that the incidence of Grade 3/4 neutropenia was ~30% in 3-weekly CDDP + RT compared with ~10–15% in weekly CDDP + RT (1,7–14). Second, auditory disorders are a problem associated with 3-weekly CDDP + RT, and weekly CDDP + RT is superior to the former due to the lower likelihood of neurotoxicity. In particular, CDDP-related auditory disorder is a dose-limiting toxicity; it occurs dose-dependently and is irreversible in most cases (15–18). In fact, in the RTOG95-01 study, the incidence of neurotoxicity including Grade 3 or more auditory disorders was 10% after 3-weekly CDDP + RT for head and neck cancer (1). In addition, in a feasibility study led by the National Cancer Center Hospital East, Grade 2 or more auditory disorder was observed in 8% of patients (7). On the other hand, there have been no reports on Grade 3 or more auditory disorders with weekly CDDP + RT. Hokkaido University and National Cancer Center Hospital East also reported that the incidence of Grade 2 or more auditory disorders was 0% in a retrospective study of weekly CDDP + RT in Japanese (8). Third, renal disorders rarely occur with weekly CDDP + RT, which is a major additional merit. In a retrospective overseas study reported by Uygun et al. (14), the incidence of Grade 3/4 renal disorder was lower with weekly CDDP + RT than with 3-weekly CDDP + RT. CDDP-related renal disorder is also dose-dependent and weekly CDDP + RT is superior in this regard. In fact, a Japanese study reported that, although no difference was observed in the incidence of Grade 3/4, the incidence of Grade 2 or more, for which dose reduction or discontinuation of CDDP must be considered, was 30–32% in 3-weekly CDDP + RT compared with 2–15% in weekly CDDP + RT, showing a significantly lower incidence with the latter (7–9). Finally, these potential merits of safety and toxicity for weekly CDDP + RT may lead to a shorter hospitalization period than for 3-weekly CDDP + RT. Therefore, we planned to test the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT.

In this randomized controlled study, we set 3-weekly CDDP + RT as the standard treatment arm and weekly CDDP + RT as the experimental treatment arm. For safety and feasibility data in Japanese post-operative high-risk patients with locally advanced SCCHN, only one feasibility study ($N = 25$) led by the National Cancer Center Hospital East is available for 3-weekly CDDP + RT. In addition, for weekly CDDP + RT, few safety and feasibility data have been accumulated in Japan, Europe and the USA Considering the above circumstances together, we evaluate the feasibility and safety of both treatment arms in the Phase II part at first and then proceed to the Phase III part to test the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT as a standard treatment.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in August 2012 and the study was activated in October 2012. This trial was registered at the UMIN Clinical Trials Registry as UMIN 000009125 [http://www.umin.ac.jp/ctr/index.htm].

PROTOCOL DIGEST OF THE JCOG 1008

Purpose

The aim of this study is to evaluate the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT for post-operative high-risk patients with locally advanced SCCHN.

Study Setting

A multi-institutional randomized Phase II/III study.

Resources

This study is supported by National Cancer Center Research and Development Funds (23-A-16 and 23-A-21).

Endpoints

The primary endpoint of the Phase II part is the proportion of treatment completion in all eligible patients. The definition of complete treatment is as follows: 3-weekly CDDP + RT arm, completion of radiation therapy within 66 days and administration of two out of three courses of 3-weekly CDDP during the radiation treatment period or within 14 days from the last day of completion of radiation; weekly CDDP + RT arm, completion of radiation therapy within 66 days and administration of five out of seven courses of weekly CDDP during the radiation treatment period.

The primary endpoint of the Phase III part is overall survival, which is defined as days from randomization to death from any cause and censored at the latest day without an event. The secondary endpoints are relapse-free survival, local relapse-free survival, nutrition-support-free survival, non-hospitalized treatment period during the permissible treatment period and adverse events. Relapse-free survival is defined as days from randomization to any disease relapse or death from any cause and censored at the latest date when the patient is alive. Local relapse-free survival is defined as days from randomization to local and regional disease relapse or death from any cause and censored at the latest date when the patient is