Table 2 Results of univariate analyses for survival after WBRT

Parameters	*n*	Median survival time (months)	6-months survival (%)	1-year survival (%)	2-year survival (%)	*p* value
Overall patients	134	5.7	43	28	12	–
Age						
<65	87	7.4	54	31	13	
≥65	47	4.9	38	22	11	0.31
Gender						
Male	69	4.5	32	17	6	
Female	65	9.1	66	40	20	0.0009
Karnofsky performance status						
≥70	95	7.9	62	39	17	
<70	39	2.2	15	3	0	<0.0001
Neurologic status						
0–1	72	7.9	58	44	22	
2–4	62	4.5	36	1	0	<0.0001
RPA criteria						
Class 1–2	96	7.9	61	37	18	
Class 3	38	2.2	16	5	0	<0.0001
Site of primary tumor						
Lung	75	7.4	55	39	21	
Others	59	4.5	39	14	2	0.001
Activity of extracranical tumor						
Absent/stable	20	9.1	60	40	25	
Progressive	114	5.2	46	26	10	0.015
Time to develop brain metastasis						
<3 months	21	16.9	75	65	40	
≥3 months	113	5.2	43	21	7	0.002
Number of brain metastasis						
1–4	40	5.1	39	21	10	
≥5	94	6.2	52	31	13	0.53
Size of the largest lesion						
<20 mm	69	7.4	53	36	16	
≥20 mm	65	5.1	42	20	8	0.11
Chemotherapeutic regimens before WBRT						
None/single	50	7.2	52	42	20	
Multiple	84	5.2	46	19	8	0.019
Chemotherapeutic regimens after WBRT						
None/single	101	4.0	33	13	4	
Multiple	33	16.4	94	73	36	<0.0001

RPA recursive partitioning analysis, *WBRT* whole brain radiotherapy

in 5 and kidney in 1. All of the histological diagnoses of lung primary patients were adenocarcinoma. Twenty-seven lung primary patients received epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) for a median duration of 7 months. Figure 3 shows the survival curve by the use of molecular-targeted therapy after

Table 3 Results of multivariate analysis for survival after WBRT

Variables	Factors	Hazard rate (95 % CI)	*p* value
Karnofsky performance status	≥70 versus <70	2.540 (1.627–3.966)	<0.0001
Gender	Female versus male	2.293 (1.541–3.412)	<0.0001
Extracranial disease status	Absent/stable versus progressive	2.134 (1.160–3.928)	0.015
Time to develop brain metastasis	<3 versus ≥3 months	1.926 (1.025–3.620)	0.042
Number of chemotherapeutic regimens after WBRT	Multiple regimens versus none/single regimen	3.406 (2.013–5.761)	<0.0001

CI confidence interval, *WBRT* whole brain radiation therapy

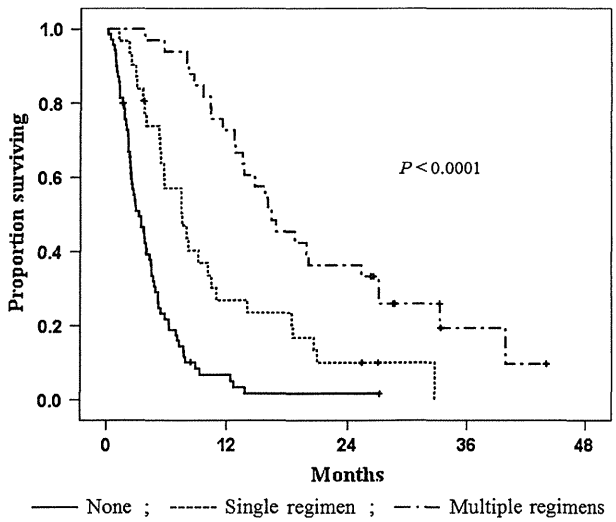

Fig. 2 Kaplan–Meier overall survival curve by the use of chemotherapeutic regimen after WBRT

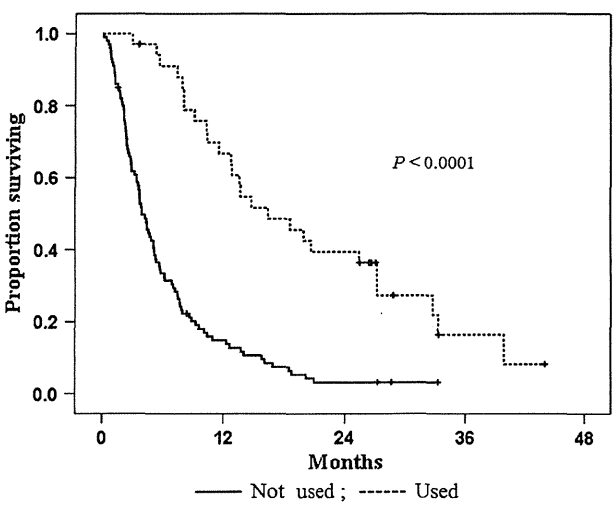

Fig. 3 Kaplan–Meier overall survival curve by the use of molecular-targeted therapy after WBRT

WBRT. The MST of the patients who received molecular-targeted therapy after WBRT was significantly longer than that of those who did not (16.4 vs. 4.0 months, $p < 0.0001$).

Discussion

Significant progress has been made over the last decades for a subset of patients with single or few brain metastases and well controlled systemic disease. In prospective randomized clinical trials, surgical resection or SRS combined with WBRT significantly prolonged survival in selected patients with single or few brain metastases (Patchell et al. 1990; Vecht et al. 1993; Andrews et al. 2004). MST of these patients who received combined therapy ranges 7–10 months. SRS alone in patients with one or few brain metastases was comparable to SRS combined with WBRT at least in terms of overall survival, with a MST of 8 months (Aoyama et al. 2006). Unfortunately, the patients who entered into these clinical trials represent only a small minority of patients with brain metastases. In clinical practice, it remains unclear whether these aggressive therapies have sufficient benefit for the majority of patients with uncontrolled systemic disease or numerous brain metastases. Currently, only WBRT is the standard treatment of choice for these patients. The indication of SRS for patients with brain metastases in clinical practice continues to be a matter of debate.

Various prospective and retrospective studies have shown that the treatment modality is the first most important prognostic factor on long-term survival, although the effect of patient selection bias is inevitable (Andrews et al. 2004; Lagerwaard et al. 1999; Patchell et al. 1990). To minimize the selection bias, we investigated only patients primarily treated with WBRT alone in this study. Numerous studies on prognostic factors in patients with brain metastases have been published previously. The results of this study re-confirmed the value of established prognostic factors reported in the literature. Multivariate analysis showed that good KPS, stable extracranial disease and female gender were independent predictors of better survival after WBRT, in line with previous literatures (Lagerwaard et al. 1999; Patchell et al. 1990; Aoyama et al. 2006; Gaspar et al. 1997; Swinson and William 2008). Dose these pretreatment characteristics fully determine the prognosis of patients with brain metastases?

Performance status is regarded as the second most important prognostic factor in patient's characteristics (Lagerwaard et al. 1999; Aoyama et al. 2006; Gaspar et al. 1997; Fleckenstein et al. 2004; 20). Generally, patients with low KPS are not indicated for aggressive therapy other than WBRT alone. In this study, the MST of the patients with KPS < 70 was only 2.2 months. The Performance status of the patients with brain metastases frequently deteriorated by extended intracranial disease. Additionally, patients with very low performance status were not indicated for further chemotherapy despite the existence of systemic disease. In this study, only 5 patients (13 %) with pre-treatment KPS < 70 received chemotherapy after WBRT. We conclude that poor survival time of the patients with low KPS is due to the systematic disease progression, as well as intracranial disease progression.

In line with our study, activity of extracranial primary disease is the third most important prognostic factor reported in the literature (Lagerwaard et al. 1999; Aoyama et al. 2006; Fleckenstein et al. 2004; 20). These finding suggests that survival of patients with brain metastases is in a large part, regulated by the extracranial status. Seventy-six patients (64 %) included in this study died due to systemic disease. This percentage is comparable to the reports of prospective clinical trials with SRS alone or SRS + WBRT for single or fewer numbers of brain metastases with well controlled systemic disease (Sneed et al. 1999; Andrews et al. 2004; Aoyama et al. 2006). This result highlights the modest effectiveness of WBRT on brain metastases. WBRT alone have adequate efficacy to avoid neurologic death for about two-thirds of patients with brain metastases. If we consider the high morbidity rate from systemic disease after WBRT, chemotherapy is the primary therapeutic approach for the control of extracranial disease. Therefore, systemic chemotherapy for chemo-responsive cancer prolongs survival despite the presence of treated brain metastases. Irradiated brain metastases will lose their prognostic significance in a large number of patients.

The role of chemotherapy in brain metastasis itself has been limited. Although there is some breakdown of blood–brain barrier (BBB) around brain metastases, the concentrations of most of the chemotherapeutic agents are still very limited within the lesion (Gerstner and Fine 2007). However, some chemotherapeutic agents are known to have activity of crossing BBB. Temozolomide (TMZ) is a third generation alkylating agent, and it can cross the BBB because of its small size and lipophilic properties (Ostermann et al. 2004). Some clinical trials suggest that single agent TMZ has some activity in patients with recurrent brain metastases (Christodoulou et al. 2001; Siena et al. 2010). Several Phase II clinical trials of TMZ combined with WBRT were performed with promising results (Antonadou et al. 2002; Addeo et al. 2008). These trials proved improved response rate and neurologic function with addition of TMZ to WBRT. A phase III clinical trial of WBRT plus SRS with or without TMZ or Erlotinib in patients with brain metastases is now ongoing (ClinicalTrials.gov identifier: NCT00096265). Patients with 1–3 brain metastases from histologically confirmed non-small cell lung cancer, well circumscribed, maximum diameter of 4 cm or less, no metastasis within 10 mm of the optic apparatus, no metastasis in the brain stem and stable extracranial metastases are enrolled. Patients are randomized to three groups: Arm 1: WBRT + SRS, Arm 2: WBRT + SRS + TMZ, Arm 3: WBRT + SRS + erlotinib. Patients in Arm 2 and 3 begin TMZ or erlotinib on the first day of WBRT and continue up to 6 months. The primary endpoint is overall survival, and secondary endpoint includes time to CNS progression, performance status at 6 months, steroid dependence at 6 months, cause of death and effect of non-protocol chemotherapy.

Topotecan is a semi-synthetic analogue of the alkaloid camptothecin, which selectively inhibits topoisomerase I. Topotecan crosses the BBB, because of its low protein binding property (Baker et al. 1996). Single agent topotecan has positive activity in patients with brain metastases from small cell lung cancer (Korfel et al. 2002). A phase III multicentric clinical trial of topotecan and WBRT for patients with brain metastases form lung cancer was planned, however, was terminated because of low patient accrual (Neuhaus et al. 2009). This trial failed to show clear benefit of adding topotecan to WBRT. Another multicentric phase III clinical trial is ongoing (ClinicalTrials.gov identifier: NCT00390806). Patients with at least one brain metastasis form non-small cell lung cancer, who have received previous chemotherapy are enrolled. Patients are randomized to two groups: experimental arm: topotecan + WBRT, control arm: WBRT alone. The primary endpoint is overall survival, secondary endpoint includes response rate, time to response, time to progression, brain tumor symptom, safety and tolerability. We think that these clinical trials for brain metastasis should evaluate the effect of non-protocol chemotherapy on survival. In the next 5 years, the results of these phase III, multicentric clinical trials will become available to further define the role of these chemotherapeutic agents when combined with WBRT and SRS, or both.

Some investigators suggest that the permeability of BBB in brain tumors can alter during or ever after fractionated radiotherapy (Yuan et al. 2006; Wilson et al. 2009; Cao et al. 2005). After irradiation, the BBB may be partially disrupted so that some chemotherapeutic agents can reach a therapeutic level in the metastatic tumors. This is another explanation of the value of systemic chemotherapy after WBRT. In fact, subset analysis of this study showed that

the use of chemotherapy after WBRT was also an independent prognostic factor predicting longer local tumor progression-free duration (data not shown). We believe that some brain metastases become sensitive to chemotherapy after irradiation. Chemo-sensitivity of brain metastases can affect the survival of a part of patients with treated brain metastases. Therefore, systemic chemotherapy will be a treatment of choice for those who have systemic disease with irradiated brain metastases. If a patient have a plan of definitive chemotherapy for primary disease after the treatment of brain metastases, such patient can be a good candidate for more aggressive therapy for brain metastases.

Another topic of debate is whether molecular-targeted therapy has a significant role on brain metastasis or not. Some investigators advocated that EGFR-TKI has promising activity on previously untreated brain metastases from lung adenocarcinoma (Wu et al. 2007; Kim et al. 2009; Katayama et al. 2009). Another investigator reported activity of trastuzumab on brain metastasis from HER2-overexpressing breast cancer (Park et al. 2009). In this study, the MST of the patients who received molecular-targeted therapy after WBRT was significantly longer than that of those who did not. In the subset analysis of this study, use of molecular-targeted therapy after WBRT was also a significant predictor of longer local progression-free duration (data not shown). We believe that molecular-targeted therapy could have some activity on the local control of some brain metastases.

Patients with "synchronous" brain metastasis survived significantly longer than "metachronous" brain metastasis patients in this study. Short time to develop brain metastasis was marginally independent prognostic factor in multivariate analysis. This is in line with a literature of surgical removal or SRS for brain metastasis (Flannery et al. 2008; Bonnette et al. 2001; Hu et al. 2006). It is easy to assume that systematic disease of patients with "synchronous" brain metastasis would more likely to respond to the following chemotherapy. The "synchronous" brain metastasis may be more sensitive to radiotherapy, when compared to brain metastasis emerged after repeated chemotherapies. Also in agreement with some literature (Lagerwaard et al. 1999; Swinson and William 2008), female patients survived significantly longer than male patients. In particular, the prognosis of female patients with brain metastasis form lung primary has reported to be significantly better than that of male patients (Lagerwaard et al. 1999; Sánchez de Cos et al. 2009). We should further continue to investigate these clinical characteristics of brain metastases.

We acknowledge that the present study had certain limitations because of its retrospective nature. First, the results of this study might be highly influenced by patient's selection bias. Patients with brain metastases which well responded to WBRT may have more opportunity for receiving multiple chemotherapy after WBRT. Second, our cohort should deviate to patients with numerous brain metastases with uncontrolled systemic disease. Because we included only patients with brain metastases primarily treated by WBRT alone, patients with poor prognosis should be negatively selected for this study. Currently, we are investigating the patients with one or few brain metastases primarily treated by SRS alone, and it will be described in another report. Actual prognostic value of chemotherapy on survival after WBRT for brain metastases should be validated in future prospective clinical trials.

Conclusions

In addition to the confirmed prognostic factors previously reported in the literature, the use of multiple chemotherapeutic regimens after WBRT was associated with better survival. Systemic chemotherapy for chemo-responsive cancer prolongs survival despite the presence of treated brain metastases. Irradiated brain metastases will lose their prognostic significance in a large number of patients. Systemic chemotherapy will be a treatment of choice for patients who have systemic disease after WBRT for brain metastases. These results should be validated in future prospective clinical trials.

Conflict of interest None.

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CLINICAL INVESTIGATION **Brain**

COMPARISON OF CLINICAL OUTCOMES OF SURGERY FOLLOWED BY LOCAL BRAIN RADIOTHERAPY AND SURGERY FOLLOWED BY WHOLE BRAIN RADIOTHERAPY IN PATIENTS WITH SINGLE BRAIN METASTASIS: SINGLE-CENTER RETROSPECTIVE ANALYSIS

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Purpose: Data comparing the clinical outcomes of local brain radiotherapy (LBRT) and whole brain RT (WBRT) in patients with a single brain metastasis after tumor removal are limited.

Patients and Methods: A retrospective analysis was performed to compare the patterns of treatment failure, cause of death, progression-free survival, median survival time, and Karnofsky performance status for long-term survivors among patients who underwent surgery followed by either LBRT or WBRT between 1990 and 2008 at the National Cancer Center Hospital.

Results: A total of 130 consecutive patients were identified. The median progression-free survival period among the patients who received postoperative LBRT ($n = 64$) and WBRT ($n = 66$) was 9.7 and 11.5 months, respectively ($p = .75$). The local recurrence rates (LBRT, 9.4% vs. WBRT, 12.1%) and intracranial new metastasis rate (LBRT, 42.2% vs. WBRT, 33.3%) were similar in each arm. The incidence of leptomeningeal metastasis was also equivalent (LBRT, 9.4% vs. WBRT, 10.6%). The median survival time for the LBRT and WBRT patients was 13.9 and 16.7 months, respectively ($p = .88$). A neurologic cause of death was noted in 35.6% of the patients in the LBRT group and 36.7% of the WBRT group ($p = .99$). The Karnofsky performance status at 2 years was comparable between the two groups.

Conclusions: The clinical outcomes of LBRT and WBRT were similar. A prospective evaluation is warranted.

Local brain radiotherapy, Whole brain radiotherapy, Single brain metastasis, Clinical outcomes, Long-term result.

INTRODUCTION

Whole brain radiotherapy (WBRT) has served as the standard of care for patients with brain metastases worldwide (1, 2). In patients with a single brain metastasis, postoperative WBRT has demonstrated better intracranial tumor control for both surgical lesions and nonsurgical new lesions and a lower rate of a neurologic cause of death compared with surgery alone (3). However, the addition of WBRT did not result in a survival benefit or extend the duration of the interval that the patients remained functionally independent. Some prospective trials, with the exception of one, and pooled analyses have clarified that a survival benefit for surgery followed by WBRT does exist compared with WBRT alone (1, 4–7). Other studies have also revealed that surgery followed by WBRT increased the duration of neurocognitive functional independence, as well as intracranial tumor control (4–6, 8, 9). Accordingly, surgery followed by WBRT has been the standard of care for patients with a single brain metastasis.

The median survival time of patients with brain metastases is considered to be approximately 2–7 months; favorable and unfavorable subgroups can be classified using recursive partitioning analysis (RPA) (10). However, about 2–8% of patients with brain metastasis can achieve longer survival periods (11, 12). Delayed WBRT toxicity, hypopituitarism, dementia, and memory disturbances influencing cognitive function have also been discussed, although the primary brain lesion is mainly responsible for the deterioration of functional independence (11, 13, 14).

Because WBRT is widely believed to induce dementia in patients with brain metastases, local brain RT (LBRT) as a substitute for WBRT has been widely accepted in some

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Table 1. Patient characteristics (n = 130)

Characteristic	All patients	Range	LBRT (n = 64)	WBRT (n = 66)	p
Age (y)	58	24–87	58 (38–87)	58 (24–79)	.35
Karnofsky performance status	70	40–100	70 (40–100)	70 (40–100)	.35
RPA class	II	I–III	II (I–III)	II (I–III)	.78*
I	40	30.8	19	21	
II	55	42.3	26	29	
III	35	26.9	19	16	
Cancer type (%)					.96*
Lung cancer	55	42.3	29	26	
Non–small-cell lung cancer	54		29	25	
Small-cell lung cancer	1		0	1	
Breast cancer	18	13.8	9	9	
Colorectal cancer	14	10.8	6	8	
Skin cancer	6	4.6	3	3	
Other	37	28.5	17	20	
Diameter of brain tumor (mm)	38	10–65	38 (10–65)	38 (15–60)	.57
Removal status					.11
Gross total removal	124	95.4	59	65	
Partial removal	6	4.6	5	1	

Abbreviations: RPA = recursive partitioning analysis; WBRT = whole brain radiotherapy; LBRT = local brain radiotherapy,
Data presented as median, with range in parentheses.
* Chi-square test.

institutions in Japan (15). LBRT delivered by linear accelerator to the tumor bed with a margin determined using the two-field technique (opposing portal irradiation) according to a dose-fractionated schedule had been applied for the treatment of single brain metastasis after surgical removal at the National Cancer Center Hospital before September 2004. This was based on the ethics that we presumed we could treat intracranial relapse using stereotactic RT after LBRT. After discussion with neurosurgeons, radio-oncologists, and medical oncologists, however, the treatment policy was changed. WBRT has been used for the treatment of all patients with single brain metastasis after tumor removal since October 2004. A Phase I-II clinical trial of postoperative LBRT was reported, and the investigators concluded that LBRT was not a suitable substitute for WBRT (16). However, that previous study included only 12 patients, and 7 of these patients died of intracranial tumor progression. The median survival time was 7.2 months, similar to that after WBRT. Another retrospective study implied that LBRT might have a similar benefit to that of WBRT in patients with a single brain metastasis (17). Bahl *et al.* (18) reported 7 cases of postoperative LBRT, of which 4 cases recurred at the same site. These studies included only a small number of patients, and any conclusions regarding the clinical outcome of postoperative LBRT, especially compared with that of postoperative WBRT, are thus difficult to make. In the present analysis, we retrospectively compared the clinical outcomes of patients with a single brain metastasis who received surgery followed by either WBRT or LBRT.

PATIENTS AND METHODS

Patient population

From the database of the neurosurgery division at the National Cancer Center Hospital, we identified patients who had undergone brain tumor removal followed by RT between 1990 and 2008. The patients were included in the present analysis if they met the following criteria: age ≥18 years, a single brain metastasis identified by magnetic resonance imaging, and tumor removal followed by either WBRT or LBRT. The exclusion criteria were as follows: extracranial malignant lymphoma or hematological tumor; brain biopsy only; previous brain RT; surgery followed by observation, with brain RT once progression was recognized; and postoperative gamma knife or linear accelerator-based radiosurgery. All the patients who received LBRT (n = 64) were treated before October 2004, and all the patients who received WBRT (n = 66) were treated after October 2004.

Data collection and definitions of terms

All the medical charts for the eligible patients were reviewed. To compare the clinical outcomes of postoperative WBRT and LBRT, we collected the following data:; preoperative magnetic resonance imaging; date of surgery and RT; RPA classification before surgery; Karnofsky performance status (KPS) at presentation; primary tumor site; date of recognition of local recurrence or intracranial new metastases; patterns of progression; leptomeningeal metastasis development; date of death; and neurologic cause of death. For the additional evaluation of long-term survivors (≥2 years after surgery), we also reviewed the KPS at 2 years after surgery.

Local recurrence was defined as recurrence at the surgical site. Intracranial new metastases included the detection of new brain metastases other than those occurring at the surgical site or the development of leptomeningeal metastases. Leptomeningeal metastases were diagnosed using a cytologic examination of cerebrospinal fluid.

Surgery and RT

The surgical indications for single brain metastasis were generally as follows: tumor diameter ≥30 mm or a tumor diameter of <30 mm with neurologic dysfunction.

Whole brain RT was administered through two lateral ports covering the brain and meninges to the foramen magnum. Normally, WBRT was delivered using a 4-MV or 6-MV linear accelerator at

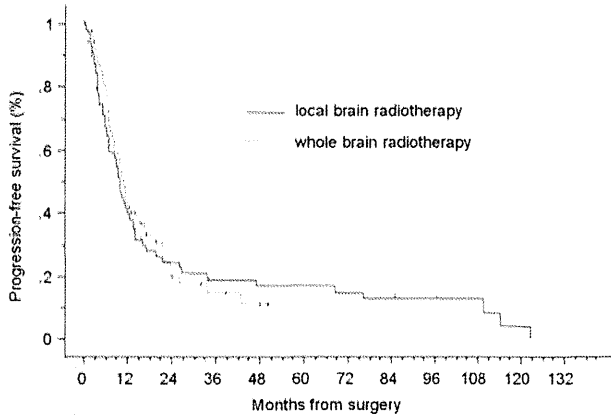

Fig. 1. Progression-free survival for patients with local brain radiotherapy (black line) and whole brain radiotherapy (dashed line).

a total dose of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. Patients who received LBRT underwent computed tomography simulation in the supine position. The clinical target volume consisted of the tumor cavity plus a 1.5-cm margin, and the planning target volume was created by expanding the clinical target volume by 0.5 cm. LBRT was administered using a 6-MV linear accelerator to the tumor bed using a two-field technique according to a dose-fractionated schedule. Normally, LBRT was delivered at a total dose of 50 Gy in 25 fractions.

Statistical analysis

Postoperative differences in local recurrence, intracranial new metastases, the development of leptomeningeal metastases, and neurologic cause of death were compared between the WBRT and LBRT groups using the Fisher exact test. Numeric data, including RPA, KPS, and age, were compared using the Mann-Whitney *U* test. Progression-free survival was defined as the interval between the date of surgery to the date of the recognition of local recurrence or intracranial new metastases. Death was treated as an event, and the absence of disease progression was treated as a censored observation on the last day of follow-up. Overall survival was defined as the interval from the date of surgery to the date of death. Patients who were lost to follow-up were treated as a censored observation on the last day of follow-up. Univariate and multivariate analyses using the Cox proportional hazard model were performed to identify relevant factors affecting survival. The numeric factors analyzed in the Cox analyses were dichotomized according to the median number. All statistical analyses were performed using StatView, version 5.0 (SAS Institute, Tokyo, Japan).

RESULTS

Of the 421 surgical cases, we identified 130 patients who met the eligibility criteria. The characteristics of these patients are listed in Table 1. Of the 130 patients, 66 had received postoperative WBRT and 64 had received postoperative LBRT. Of the 66 patients who had received WBRT, 34 (51.5%) were treated to a dose of 30 Gy delivered in 10 fractions, and 31 (47.0%) were treated to a dose of 37.5 Gy delivered in 15 fractions. Of the 64 patients who received LBRT, 57 (89.1%) were treated to a dose of 50 Gy in 25 fractions, and 7 were treated with a variety of dose-fractionation schedules (24 Gy in 12 fractions to 60 Gy in 30 fractions).

The median progression-free survival period for the patients who received postoperative LBRT and WBRT was 9.7 and 11.5 months, respectively ($p = .75$; Fig. 1). The patients who underwent LBRT and WBRT developed 33 and 30 recurrences, respectively. The local recurrence rates (9.4% vs. 12.1%) and intracranial new metastases rates (42.2% vs. 33.3%) were not significantly different between the LBRT and WBRT groups (Table 2). The incidence of leptomeningeal metastases in patients receiving LBRT and WBRT was 9.4% and 10.6%, respectively ($p = .99$).

The median survival time for patients who received postoperative LBRT and WBRT was 13.9 and 16.7 months, respectively ($p = .88$; Fig. 2). Of the 64 patients who received LBRT and the 66 patients who received and WBRT, 59 and 49 died, respectively. A neurologic cause of death was noted in 35.6% of the patients in the LBRT group and 36.7% of the patients in the WBRT group ($p = .99$; Table 2). Univariate analyses revealed that only the RPA classification correlated significantly with survival (hazard ratio [HR], 0.436; $p = .002$). In particular, RT (LBRT vs. WBRT) did not correlate with survival (HR, 1.031; $p = .88$; Table 3). Multivariate analyses revealed that RPA was the only significant factor associated with survival (HR, 0.399; $p = .001$). Neither LBRT nor WBRT was related to survival (HR, 0.933; $p = .74$; Table 4).

Table 2. Patterns of treatment failure in patients who received WBRT and LBRT

Variable	LBRT ($n = 64$)	WBRT ($n = 66$)	
Total recurrences identified *(n)*	33	30	*p*
Local recurrence	6 (18.2)	8 (26.7)	.61
Distant metastasis	27 (81.8)	22 (73.3)	.61
Development of leptomeningeal metastases *(n)*	6	7	.99
Total deaths identified *(n)*	59	49	
Neurologic cause of death	21 (35.6)	18 (36.7)	.98*
Other	21 (35.6)	17 (34.7)	
Unknown	17 (28.8)	15 (30.6)	

Abbreviations: WBRT = whole brain radiotherapy; LBRT = local brain radiotherapy.
Data in parentheses are percentages.
* Chi-square test.

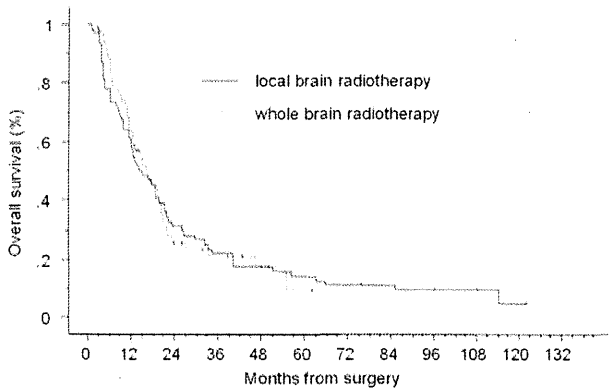

Fig. 2. Overall survival in patients with local brain radiotherapy (black line) and whole brain radiotherapy (dashed line).

We further analyzed the patterns of RT after recurrence in patients who received either postoperative LBRT or WBRT. Of the 33 patients who developed recurrences after postoperative LBRT, additional RT was performed in 15 (45.5%). Of the 15 patients, 6 underwent gamma knife or linear accelerator-based radiosurgery. LBRT was performed in 5 patients, and 4 received WBRT. Of the 30 patients who developed recurrences after postoperative WBRT, 16 (53.3%) received additional RT. Of the 16 patients, 13 received gamma knife or linear accelerator-based radiosurgery, and 3 received LBRT.

Among the patients who survived for >2 years, we compared the KPS at 2 years after surgery. A total of 20 patients who had received postoperative LBRT and 13 who had received postoperative WBRT were identified. The median KPS score at 2 years for these patients in the LBRT and WBRT groups was 80 (range, 60–100) and 80 (range, 60–100; $p = .99$), respectively. Of the 20 patients who had received LBRT, 9 experienced relapse in a local lesion, 2 had focal signs without relapse, which might have indicated radiation necrosis, and 7 had been well without relapse. For 2 other patients, this information was not available.

DISCUSSION

We have revealed the clinical outcomes of postoperative LBRT among patients with single metastasis and compared them with those of patients who underwent postoperative WBRT. The clinical outcomes, including progression-free survival, overall survival, local recurrence, intracranial new metastases, development of leptomeningeal metastases, and neurologic cause of death, were not significantly different between the two groups. In an analysis of relapse patterns, the patients treated with LBRT tended to have a lower probability of developing local recurrence (9.4% vs. 12.1%) and a greater probability of developing intracranial new metastases (42.2% vs. 33.3%), although these values were not significantly different. The probability of developing leptomeningeal metastases was also similar in each group (9.4% vs. 10.6%).

Previous reports have indicated that the addition of WBRT after tumor removal significantly reduces the local recurrence rate (3, 9). However, approximately 6–50% of patients develop relapses at new intracranial sites in the brain (5, 9, 19). Furthermore, about 20–30% of patients with brain metastasis die of neurologic causes even if a radiation boost has been added using stereotactic radiosurgery to increase local control, although the presence of extracranial lesions is the strongest factor for predicting survival (7, 20, 21). In our study, intracranial new metastases were predominant in both groups. The frequency of intracranial recurrence (new local and intracranial metastases) was somewhat greater than in previous series, although the rate of a neurologic cause of death was equivalent. Importantly, the patterns of treatment failure were similar in the LBRT and WBRT groups. Muacevic *et al.* (22) insisted that postoperative WBRT should be applied in patients with a single brain metastasis to destroy so-called micrometastases, based on the results of their randomized trial. They compared patients with a small single metastasis who received either surgery plus WBRT or gamma knife surgery alone. Their sample size was underpowered, although the risk of intracranial new metastases seemed to be lower in the WBRT cohort. To date, no randomized trials comparing the clinical outcomes of postoperative WBRT and postoperative gamma knife or linear accelerator-based radiosurgery, or LBRT have been reported.

We have demonstrated a similar efficacy for LBRT and WBRT. WBRT has problems in terms of delayed toxicity developing leukoencephalopathy, although the number of long-term survivors with brain metastasis seems to be somewhat low (11, 12). LBRT might be beneficial with regard to the protection of normal brain tissue. We compared the KPS

Table 3. Univariate analyses regarding survival

Variable	HR	95% CI	*p*
RT (LBRT vs. WBRT)	1.031	0.698–1.523	.88
RPA classification			
I vs. III	0.436	0.259–0.733	.002
II vs. III	0.808	0.514–0.127	.35
Removal status (gross total removal vs. partial removal)	0.948	0.385–2.334	.91
Tumor diameter (≥38 vs. <38 mm)	1.053	0.718–1.543	.79
Cancer type (lung cancer vs. other)	0.694	0.470–1.025	.062

Abbreviations: RT = radiotherapy; HR = hazard ratio; CI = confidence interval; other abbreviations as in Table 1.

Table 4. Multivariate analyses regarding survival

Variable	HR	95% CI	*p*
RT (LBRT vs. WBRT)	0.933	0.614–1.416	.743
RPA classification			
I vs. III	0.399	0.232–0.688	.001
II vs. III	0.736	0.455–1.191	.22
Removal status (gross total removal vs. partial removal)	0.622	0.239–1.615	.33
Tumor diameter (≥38 vs. <38 mm)	0.852	0.559–1.297	.45
Cancer type (lung cancer vs. other)	0.662	0.438–1.001	.05

Abbreviations as in Tables 1 and 3.

at 2 years to examine any delayed toxicity. Because of the nature of the present retrospective study, the detailed neurocognitive function or quality of life of the patients could not be identified. Among the long-term survivors, however, the KPS was preserved in both treatment groups. Thus, LBRT might be indicated for elderly patients at risk of developing dementia if LBRT has the same ability to control primary brain tumors, which is considered to be the main factor affecting neurocognitive function (14).

The present study had some limitations because of its retrospective nature. First, the radiation dose varied. About 90% of the LBRT patients received a dose of 50 Gy delivered in 25 fractions, and approximately 50% of the WBRT patients received a dose of 30 Gy delivered in 10 fractions; the others received a dose of 37.5 Gy delivered in 15 fractions. According to the summary by Tsao *et al.* (1), no differences in terms of survival or neurocognitive function were observed among the various dose-fraction schedules of WBRT. Second, the present study was a historical case-control study comparing LBRT and WBRT. Patients at risk of developing multiple metastases might have undergone WBRT during the period before 2004, when we started performing WBRT as the standard of care. Thus, the patients who were treated with LBRT might have had better general condition compared with the patients who were treated with WBRT. We compared the baseline characteristics of each treatment arm and used multivariate analyses to reduce any potential biases.

CONCLUSIONS

We have demonstrated the clinical efficacy of LBRT compared with WBRT on a large scale. The clinical outcomes, including progression-free survival, overall survival, patterns of treatment failure, development of leptomeningeal metastases, and a neurologic cause of death, were similar in both treatment groups. The KPS at 2 years was also similar when the two groups were compared. This result should be evaluated in a prospective manner.

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original article

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Compliance with Good Clinical Practice in oncology registration trials in Japan

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Background: This study aimed to examine the quality in oncology registration trials for new drug application (NDA) or supplemental new drug application (sNDA) as extensions of the indications for use in Japan based on Good Clinical Practice (GCP) audit findings.

Materials and methods: We collected audit reports of on-site GCP inspections for registration trials in 383 NDAs or sNDAs that were reviewed by the Pharmaceuticals and Medical Devices Agency between the fiscal years 2004 and 2009.

Results: Among the 40 audits for oncology drug applications, the frequencies at which one or more deficiencies ascribed to institution, investigator, sponsor, and institutional review board were found to be 15 (37.5%), 13 (32.5%), 21 (52.5%), and 10 (25.0%), respectively. The exclusion of patients from the review objective due to serious violations of GCP in 40 audits for oncology drug applications was observed in 2 (5.0%) cases, whereas that in the remaining 343 audits for other drug applications was observed in 40 (11.7%) cases.

Conclusion: The overall compliance of GCP in oncology registration trials was moderately better than that in registration trials for other diseases, although there was no statistically significant difference between them.

Key words: audit, cancer, compliance, Good Clinical Practice, inspection, registration trial

introduction

Approval of new drug applications (NDA) or supplemental new drug applications (sNDA) for extension of the range of indication and/or posology as well as the method of administration is based on collecting evidential materials from registration trials that are strictly managed in terms of quality control and quality assurance. The registration trials for applications are conducted in conformity with Good Clinical Practice (GCP) that provides corroboration of both ethics and science. The purpose of GCP is to protect the human rights and safety of the subjects and is based on the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subject in order to ensure accurate data and reliability in registration trials [1]. The Ministry of Health and Welfare [currently Ministry of Health, Labour and Welfare (MHLW)] of Japan had issued instructions regarding the old GCP guideline in October 1990, which was not legally binding [2]. In April 1997, a new GCP guideline was enforced in response to the implementation of the GCP released by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use for all Japanese registration trials that began from April 1998 onward [3, 4]. Major differences between the old and new GCP guidelines are related to the acquisition of written informed consent documents, intensification of the responsibility of the sponsor, clarification of the responsibility and role of the principal investigator, and improvements in the function of the institutional review board (IRB) and supports for registration trials [2, 3].

In Japan, the number of clinical trial protocol notifications for oncology drug applications is rapidly increasing with each passing year; oncology drug applications comprised ~15% of all clinical trial protocol notifications in the fiscal year 2007 [5]. The number of clinical trial protocol notifications among global registration trials has been increasing substantially; moreover, clinical trial protocol notifications for oncology drugs comprised 59% of global clinical trial protocol notifications, making it the largest field in drug applications in the fiscal year 2007 [6]. It appears that clinical development in the oncology drug field became both active and stable in Japan around this time. These conditions have also made it easier to carry oncology registration trials with sufficient quality according to GCP as compared with that in other drug fields.

Clinical trials for oncology drugs have many differentiating features as compared with those for other drugs. In oncology clinical trials, complicated inclusion/exclusion criteria, frequent dose modifications caused by toxic effects, numerous

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prohibited concomitant medications, tight schedules of clinical assessments, and long follow-up periods are required. In addition, since the pharmacological effects of oncology drugs generally influence cell proliferation or cell division, a large number of adverse events are frequently reported in oncology clinical trials as compared with clinical trials for other drugs. Thus, enormous effort and responsibility are imposed on trial participants, such as institutions, investigator, IRBs, and sponsors.

In this study, we examined GCP compliance in oncology registration trials in order to ensure high-quality clinical trials in Japan. The GCP compliance of the registration trials for NDA and sNDA was examined based on the Pharmaceuticals and Medical Devices Agency's (PMDA) judgment on recent overall results of on-site GCP audits. We have discussed the quality of oncology registration trials through a comparison of the deficiencies found in GCP inspections that were ascribed to the institution, investigator, sponsor, and IRB between 40 oncology drugs applications and 343 drug applications for other diseases.

materials and methods

GCP inspection of PMDA in Japan

The Office of Conformity Audit of PMDA carried out GCP inspections that consisted of document-based conformity audit at the PMDA along with on-site GCP audits [7]. The document-based conformity audit exhaustively inspects the consistency between application materials attached to the application form for approval and all evidential materials of all institutions retained by study sponsors (e.g. case report forms, monitoring records, etc.) from the viewpoint of Good Laboratory Practice, GCP, and conformity criteria of the application materials. The on-site GCP audit inspects the consistency between raw data (e.g. medical records, examination slips, and patient diaries) as evidential materials of surveyed medical institutions and evidential documents of surveyed institutions held by study sponsors (e.g., case report forms). In addition, the on-site GCP audit inspects the general institutional structure for registration trials at the institution (e.g. administration of the medical institution, IRB, maintenance of essential archives, and investigational drug accountability of the pharmacy). The objectives of on-site GCP audits in trial applications have been previously defined [8]. On-site GCP audits are generally carried out for four institutions in NDA and two institutions in sNDA. An institution in Japan or another country enrolling many patients into a pivotal registration trial of application is selected for on-site GCP audit. The PMDA finally judges GCP compliance as follows: conformation, conformation with proviso, or nonconformation. The results are sent to both the sponsor and the institution.

Conformation indicates complete compliance with the GCP in the registration trial for the application. Conformation with proviso means that the PMDA imposes the exclusion of patients from the review objective due to serious violations of the GCP and evaluates the registration trial comprising the remaining patients. If a critical GCP violation concerning ethics and/or science in the registration trial is found, the PMDA judges that all the materials in the registration trial related to GCP nonconformation should be deleted from the application for NDA or sNDA. In this case, the PMDA generally concludes in favor of rejection of the application. It should be noted that when the PMDA's judgment is nonconformation, these results are not publicly released; therefore, the frequency of nonconformations is not investigated.

data sources

In Japan, for each application, on-site GCP inspection for the registration trials—including trials conducted in Japan and overseas for the drugs—are conducted, and their comprehensive audit results are publicly released with exposures of the deficiencies found in GCP inspections that are ascribed to the institution, investigator, sponsor, and IRB [9]. In this study, 344 audits, which were reviewed by the PMDA and approved by the MHLW of Japan between April 2004 and March 2010 (fiscal years 2004 to 2009), were examined, excluding public domain approvals and audits without on-site GCP inspections [10]. For each audit, the following data were collected: medicinal classification of the approved drug, approval year, the PMDA's judgment on GCP compliance (conformation with/without proviso), the number of patients excluded due to serious violations of GCP, GCP deficiencies, and responsible participants of deficiencies (institution, investigator, sponsor, and IRB).

Fisher's exact test was used to compare the frequency distributions with respect to the deficiencies between the audits for anticancer drugs and those for other diseases. A two-sided $P \leq 0.05$ was considered to be statistically significant. All the analyses were carried out using the SAS software (version 9.1; SAS Institute Inc., Cary, NC).

results

conformation with/without proviso

The approval years and medicinal classifications for 383 audits are shown in Table 1. The audits for oncology drug applications comprised 40 (10.4%) of the 383 audits.

Table 2 shows the proportions of conformation with/without proviso overall and for each medicinal classification. Overall, 89.6% of conformation and 10.4% of conformation with proviso were observed. Among the 42 audits judged as conformation with proviso, the frequencies of audits with ≥1 deficiencies ascribed to the institution, investigator, IRB, and sponsor were 34 (81.0%), 23 (54.8%), 12 (28.6%), and 25 (59.5%), respectively. Additionally, the frequencies of audits in each deficiency ascribed to each responsible participant are shown in Table 3.

Conformation with proviso in 40 audits for anticancer drug applications were observed in 2 (5.0%) cases, whereas that in the remaining 343 audits for the other disease applications was observed in 40 (11.7%) ($P = 0.286$). The proportion of conformation with proviso in cancer registration trials tended to be smaller than that in the registration trials for other disease applications, although the number of audits varied depending upon the medicinal classification. Furthermore, although the number of excluded patients was unknown in 9 audits, among the 42 audits judged as conformation with proviso, the median number of excluded patients was 3 (range 1–182) in the remaining 33 audits.

responsible participants due to deficiencies

Table 4 shows the distributions of audits in which one or more deficiencies were ascribed to the responsible participants overall and in each medicinal classification. The proportion of approvals with ≥1 deficiencies ascribed to the institution, investigator, IRB, and sponsor were 15 (37.5%), 13 (32.5%), 10 (25.0%), and 21 (52.5%) in 40 audits, respectively, for oncology drug applications and 168 (49.0%), 145 (42.3%), 78 (22.7%), and 169 (49.3%),

Table 1. Summary of 383 registration trial approvals [*n* (%)]

Medicinal classification	Approval year, fiscal year						Total
	2004	2005	2006	2007	2008	2009	
Neurological	1 (4.2)	3 (7.3)	8 (12.3)	10 (10.9)	8 (11.0)	17 (19.3)	47 (12.3)
Metabolic	1 (4.2)	6 (14.6)	12 (18.5)	15 (16.3)	18 (24.7)	17 (19.3)	69 (18.0)
Oncology	2 (8.3)	7 (17.1)	6 (9.2)	8 (8.7)	9 (12.3)	8 (9.1)	40 (10.4)
Cardiovascular	3 (12.5)	3 (7.3)	4 (6.2)	7 (7.6)	10 (13.7)	9 (10.2)	36 (9.4)
Respiratory	1 (4.2)	1 (2.4)	1 (1.5)	2 (2.2)	0 (0.0)	5 (5.7)	10 (2.6)
Gastrointestinal	0 (0.0)	1 (2.4)	3 (4.6)	10 (10.9)	2 (2.7)	6 (6.8)	22 (5.7)
Hormonal	2 (8.3)	3 (7.3)	7 (10.8)	6 (6.5)	8 (11.0)	7 (8.0)	33 (8.6)
Urological	2 (8.3)	1 (2.4)	4 (6.2)	5 (5.4)	3 (4.1)	1 (1.1)	16 (4.2)
Antimicrobial	7 (29.2)	7 (17.1)	10 (15.4)	16 (17.4)	4 (5.5)	9 (10.2)	53 (13.8)
Biologics	2 (8.3)	4 (9.8)	5 (7.7)	6 86.5)	5 (6.8)	7 8.0)	29 (7.6)
Others	3 (12.5)	5 (12.1)	5 (7.7)	7 (7.6)	6 (8.2)	2 (2.3)	28 (7.3)
Total	24 (100)	41 (100)	65 (100)	92 (100)	73 (100)	88 (100)	383 (100)

Table 2. PMDA's judgment on GCP compliance in oncology and other drug audits [*n* (%)]

Judgments	Medicinal types		Total
	Oncology	Others	
Conformation (without proviso)	38 (95.0)	303 (88.3)	341 (89.6)
Conformation with proviso	2 (5.0)	40 (11.7)	42 (10.4)

Fisher's exact test for contingency table of judgments and medicinal types: $P = 0.286$.

GCP, Good Clinical Practice; PMDA, Pharmaceuticals and Medical Devices Agency.

respectively, in the remaining 343 audits for other drug applications. The deficiencies ascribed to the institution and investigator in the cancer registration trials tended to be lesser than those in the registration trials for other diseases ($P = 0.184$ for institution and $P = 0.309$ for investigator).

deficiencies ascribed to responsible participants

Table 5 shows the frequencies of audits in each deficiency ascribed to each responsible participant overall and in each medicinal classification. The deficiencies related to archives, eligibility criteria, and prohibited concomitant therapies in 40 audits for oncology drug applications were 1 (2.5%), 2 (5.0%), and 0 (0.0%), respectively, whereas those in the 308 other drug audits were 47 (13.7%), 43 (12.5%), and 28 (8.2%), respectively ($P = 0.043$ for archives, $P = 0.201$ for eligibility criteria, and $P = 0.099$ for prohibited concomitant therapies). On the other hand, the deficiency of 'insufficient review' by the IRB in 40 audits for oncology drug applications was higher than that in the 343 other drug audits (17.5% versus 5.5%, $P = 0.012$).

discussion

The results of the present study indicated that the overall compliance of GCP in oncology registration trials was passably better than that in registration trials for other diseases, although there was no statistically significant difference between them. According to Table 5, the problems related to archives in institutions were lesser but insufficient reviews by the IRB were more frequent in the oncology drug applications when compared with those for other diseases. Therefore, completeness of IRB reviews would enhance quality of drug applications in the oncology field.

Previous studies have analyzed a number of GCP deficiencies in registration trials for NDA or sNDA, approved by the MHLW of Japan, from the fiscal year 1997 to 2006 [11–18]. Since a white paper or annual report regarding the overall results of on-site GCP audit has not been officially published, these studies have repeatedly used the same data that were partly released by the PMDA, workshops, or symposiums. In addition, most of these studies examined GCP deficiencies immediately after the enforcement of the new GCP guidelines [11–15]. The examination of compliance with GCP in registration trials for NDA or sNDA in recent times is required.

Our study demonstrated 10.4% of conformations with proviso in registration trials overall in the past 5 years. Previous studies have reported that conformations with proviso comprised 17.6% of registration trials during the fiscal years 2001 and 2003 [16]. Based on the results of the present study and those of previous studies, compliance with GCP in Japanese registration trials has generally been improving [16, 17]. Furthermore, the present study revealed the overall GCP compliance of oncology registration trials tended to be better than that of registration trials for other drugs.

The present study revealed trial institution deviations, investigator deviations, and sponsor deviations in 40%–50% of the audits. The frequencies of deviations related to the trial institution or investigator were lower in the oncology registration trials as compared with those in the other drug registration trials. This may be because the development of oncology drugs is highly specialized; therefore, research sources—including the trial institution, investigator, and other health care professionals—for the registration trials of oncology drugs have much greater experience and can carry registration trials with greater compliance.

Table 3. Frequencies of audits in each deficiency ascribed to each responsible participant in 42 approvals judged as conformation with proviso

Responsible participants	Deficiencies	*n* (%)
Institution	Qualification requirements of hospitals were not met	6 (14.3)
	Lack of appropriate SOP	0 (0.0)
	All investigators were not identified in the contract	0 (0.0)
	Inappropriate contract	6 (14.3)
	Inappropriate informed consent	11 (26.2)
	CRFs filled incorrectly/and or insufficiently	8 (19.1)
	Problems related to archives	19 (45.2)
	Delay in communication of safety information	3 (7.1)
	Others	6 (14.3)
Investigator	Eligibility criteria were not met	13 (31.0)
	Prohibited concomitant therapies	7 (16.7)
	Laboratory tests were not performed according to the defined protocol	9 (21.4)
	Nonobservance of dose and/or schedule provided by the protocol	8 (19.1)
	Others	8 (19.1)
Sponsor	Inappropriate monitoring	24 (57.1)
	Delay in communication of safety information to institution	4 (9.5)
	Others	2 (4.8)
IRB	Qualification requirements of IRB were not met	2 (4.8)
	Lack of appropriate SOP	1 (2.4)
	Insufficient review	4 (9.5)
	Insufficient minutes of meetings	2 (4.8)
	Others	7 (16.7)

IRB, institutional review board; SOP, standard operational procedure; CRFs, case report forms.

Table 4. Frequencies of audits in which one or more deficiencies ascribed to the responsible participants were found by GCP inspection in oncology and other registered trials [*n* (%)]

Responsible participants	Medicinal type		Total	*P* value[a]
	Oncology	Others		
Institution				0.184
Yes	15 (37.5)	168 (49.0)	183 (47.8)	
No	25 (62.5)	175 (51.0)	200 (52.2)	
Investigator				0.309
Yes	13 (32.5)	145 (42.3)	158 (41.3)	
No	27 (67.5)	198 (57.7)	225 (58.8)	
IRB				0.696
Yes	10 (25.0)	78 (22.7)	88 (23.0)	
No	30 (75.0)	265 (77.3)	295 (77.0)	
Sponsor				0.740
Yes	21 (52.5)	169 (49.3)	190 (49.6)	
No	19 (47.5)	174 (50.7)	193 (50.4)	

[a]Fisher's exact test for contingency table of the presence of deficiencies ascribed to each responsible participant and medicinal types.
GCP, Good Clinical Practice; IRB, institutional review board.

Drug development generally takes considerably long due to the on-site GCP audit in response to a trial application. However, problems related to archives would essentially relate to the reliability of the registration trial regarding the existing subjects, ethics, and science. We noted no problems related to archives in the oncology drug registration trials; the frequency of this deficiency was clearly lower for oncology drugs as compared with other drugs. Thus, the compliance with GCP regarding archives was satisfactory in oncology drug registration trials.

The frequency of protocol deviation in oncology fields is lower than that for other medicinal classifications; however, protocol deviations for eligibility criteria or use of prohibited concomitant therapies would influence subject safety in registration trials. Therefore, investigators, clinical research coordinators (CRC), and other health care professionals who support registration trials should make an effort to have sufficient knowledge regarding the target disease and treatment and keep track of details regarding the protocol and GCP. The incidence of deficiencies at domestic investigational sites with CRC was 21% ($N = 270/1260$), which was lower than that of deficiencies at domestic investigational sites without CRC, i.e. 58% ($N = 188/325$) [7, 18]. Therefore, an effective approach for reducing deficiencies associated with protocol deviation would entail the careful selection of trial institutions with sufficient numbers of well-trained CRCs and suitable conditions for carrying out monitoring.

In the present study, deficiencies in monitoring were most frequent both overall and in sponsor deviations. Monitoring of the medical institution by the sponsor is enforced by GCP in order to ensure appropriate operation of the registration trial according to trial protocol and GCP. A previous study indicated that typical monitoring issues associated with sponsors in the fiscal year 2005 were as follows: operation of monitoring associated with standard operation procedure and source document verification (41%), timing of monitoring (9.5%), taking appropriate precautions to prevent deviation by monitoring report (8.5%), submission of monitoring report (5.5%), and other (35.5%) [18]. Appropriate monitoring for registration trial by a monitor who has been specifically trained and possesses scientific and clinical knowledge is important for ensuring quality control and quality assurance of registration trials. For further improvement in reducing deficiencies in monitoring, the monitor in the sponsor organization or contract research organization (CRO) should be sufficiently familiar with the protocol and GCP. Improved performance of various parties in the registration trial would not only facilitate operation of the registration trial by the sponsor but also the operation of investigator-initiated registration-directed clinical trials by the investigator, according to the revised GCP enforced from July 2003 [19].

Another major item of deficiency related to the sponsor is a delay in communicating information regarding adverse drug reactions; this is related to subject safety, ethics, and operation of the registration trial. A seamless communication system for delivering critical information is important for ensuring subject safety and appropriate operation of the registration trial. In

Table 5. Frequencies of audits in which each deficiency was found by GCP inspection in oncology drug and other drug applications [*n* (%)]

Responsible participants	Deficiencies	Oncology	Others	Total	*P* value[a]
Institution	Qualification requirements of hospitals were not met	1 (2.5)	6 (1.8)	7 (1.8)	0.541
	Lack of appropriate SOP	0 (0.0)	0 (0.0)	0 (0.0)	–
	All investigators were not identified in the contract	0 (0.0)	3 (0.9)	3 (0.8)	1.000
	Inappropriate contract	2 (5.0)	17 (5.0)	19 (5.0)	1.000
	Inappropriate informed consent	3 (7.5)	26 (7.6)	29 (7.6)	1.000
	CRFs filled incorrectly/and or insufficiently	8 (20.0)	81 (23.6)	89 (23.2)	0.696
	Problems related to archives	1 (2.5)	47 (13.7)	48 (12.5)	0.043
	Delay in communication of safety information	2 (5.0)	21 (6.1)	23 (6.0)	1.000
	Others	4 (10.0)	36 (10.5)	40 (10.4)	1.000
Investigator	Eligibility criteria were not met	2 (5.0)	43 (12.5)	45 (11.8)	0.201
	Prohibited concomitant therapies	0 (0.0)	28 (8.2)	28 (7.3)	0.099
	Laboratory tests were not carried out according to the defined protocol	6 (15.0)	59 (17.2)	65 (17.0)	0.823
	Nonobservance of dose and/or schedule provided by the protocol	5 (12.5)	23 (6.7)	28 (7.3)	0.195
	Others	5 (12.5)	48 (14.0)	53 (13.8)	1.000
IRB	Qualification requirements of IRB were not met	1 (2.5)	5 (1.5)	6 (1.6)	0.487
	Lack of appropriate SOP	0 (0.0)	2 (0.6)	2 (0.5)	1.000
	Insufficient review	7 (17.5)	19 (5.5)	26 (6.8)	0.012
	Insufficient minutes of meetings	0 (0.0)	12 (3.5)	12 (3.1)	0.623
	Others	2 (5.0)	49 (14.3)	51 (13.3)	0.138
Sponsor	Inappropriate monitoring	19 (47.5)	136 (39.7)	155 (40.5)	0.395
	Delay in communication of safety information to institution	5 (12.5)	50 (14.6)	55 (14.4)	1.000
	Others	1 (2.5)	13 (3.8)	14 (3.7)	1.000

[a]Fisher's exact test for contingency table of the presence of each deficiency and medicinal types.
GCP, Good Clinical Practice; IRB, institutional review board; SOP, standard operational procedure.

recent drug development protocols, registration trials such as randomized clinical trials are carried out globally in various trial institutions; in such a scenario, worldwide regional offices of the sponsor would be ideal for improving communication systems and ensuring smooth and timely communication.

There have been various approaches for improving social and scientific infrastructure for clinical research in Japan by academia, industry, and the government. In 2003, the MHLW drew up and published the nationwide 3-year clinical trial activation plan, under which it promoted various measures, including the creation of clinical trial networks and fostering of CRC. Subsequently, the MHLW created the office of clinical trial promotion, research, and development and launched the new 5 yearly clinical trial activation plan in 2007, which was expected to reinforce clinical research infrastructure to ensure patient safety and to secure access to new drugs and devices [20]. Furthermore, the MHLW science research grants 'research on clinical trials infrastructure development' were inaugurated to support framework development for promoting clinical trials (comprising grants to 10 leading academic medical centers). Thus, a study on 'the development of individual health care institution infrastructure models aimed at equally sharing cancer research infrastructure development' was started, and it became possible to pursue favorable institutional infrastructure development and human resources training concerning the ethical aspects of clinical research and methods of new drug development in the National Cancer Center Hospital [21, 22]. Furthermore, the Japanese Ministry of Education, Culture, Sports, Science and Technology provided grants to five universities and a clinical research organization named 'Coordination, Support and Training Program for Translational Research' in 2007 and onward [22, 23]. These various approaches promoted the establishment of a clinical trial infrastructure; we believe that an adequate infrastructure would be the optimal influence for ensuring compliance with GCP in registration trials.

Our study had certain limitations. We were not able to use the full data of on-site GCP audits for a number of trial institutions—such as the trial institution background, i.e. scale (university hospital, national hospital, private hospital, and clinic), region (Japan or other countries), number of subjects under on-site GCP audit, presence of supporting system for registered trial (CRC, site management organization, CRO, etc.)—because the PMDA review reports for on-site GCP audit are the only available data source and these do not have detailed data. Therefore, it is difficult to directly compare the results of the present study with those of previous studies. Because there

are few reports of on-site GCP audits by regulatory agencies, the present study described differences in deficiencies from on-site GCP audits between Japan and other countries. For further improving global compliance with GCP, we consider that each regulatory agency should disclose detailed results of on-site GCP audits on a regular basis.

GCP inspections have indicated certain deficiencies in the data of registration trials and the operation systems of registration trials; these were evaluated in the regulatory reviews of NDA or sNDA. However, the most important purpose of GCP inspection is to prevent a recurrence of GCP deficiencies for establishing higher quality in drug development. In 2009, the European Medicines Agency (EMEA) and the Food and Drug Administration (FDA), USA, initiated the EMEA–FDA GCP initiative that focuses upon enhanced and systematic GCP-related information exchanges between the EMEA and FDA combined with collaboration in the conduct of GCP inspections of registration trials [24]. The results of the present study suggest that the principle of compliance with GCP for registration trials has reached Japanese investigators and trial institutions, and high-quality GCP inspections are thereby being carried out by the PMDA. The clinical development of medicines is a global undertaking. Therefore, in the future, we consider it important that all regulatory agencies work in a collaborative and synergistic manner in order to achieve a system for the optimal use of GCP inspection resources and results and implement information exchanges.

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