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INTRODUCTION TO REVIEW ARTICLES

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Treatment of metastatic brain tumors

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The number of patients with metastatic brain tumors has been increasing because of advances in less invasive imaging modalities such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), improvements in the treatment of extracranial cancers, and the increase of the elderly population. According to the Central Brain Tumor Registry of the United States, the incidence of primary brain tumors is 16.5 cases per 100000 person-years.[1] On the other hand, cancers are detected in 400 persons per 100000 population and of these individuals, 30% or 40% have metastatic brain tumors. This means that the incidence of metastatic brain tumors is estimated to be seven to nine times as high as that of primary brain tumors.

The diagnosis of metastatic brain tumors is usually made by MRI. Most of these tumors show isointensity on T1-weighted images (T1WI) and are highly enhanced by gadolinium-diethylenetriaminepentaacetic acid (DTPA). They are usually round-shaped and the central area shows low intensity on T1WI due to necrosis or fluid collection. Multiplicity is another characteristic of metastatic brain tumors; however, some glioblastomas and malignant lymphomas form multiple intracranial enhancing lesions. The final diagnosis should be made by biopsy if possible.

The prognosis of patients with metastatic brain tumors is poor and most of them have been treated only by irradiation of the whole brain. According to a recursive partitioning analysis of 1200 patients enrolled in three Radiation Therapy Oncology Group (RTOG) clinical trials (RTOG 79-16; 85-28; 89-05), patients with metastatic brain tumors could be classified into three groups. Class 1 includes patients with a Karnofsky performance status (KPS) of 70 or less, age less than 65 years,, controlled primary tumor, and no metastases except in the brain. Class 3 includes patients with a KPS below 70, while all other patients are classified as class 2. The median survivals in classes 1, 2, and 3 were 7.1, 4.2, and 2.3 months, respectively.[2]

On the other hand Patchell et al.[3] reported the significance of surgery for brain metastases. They randomized patients with a solitary brain metastasis into two groups, those receiving whole-brain radiotherapy (WBRT) and those receiving WBRT after craniotomy. The median survival of the WBRT group was only 8 weeks, while that of the surgery + WBRT group was 40 weeks; local recurrence appeared in 52% of the WBRT group and in 20% of the surgery + WBRT group.[3]

Stereotactic radiosurgery (SRS) was introduced for the treatment of brain metastases and has now been used for 20 years. A combination of SRS and WBRT showed better local control than WBRT alone, but longer survival compared with that in the WBRT group was obtained in only a limited subset of patients.[4] It is well known that WBRT influences the cognitive function of patients, and the non-inferiority testing of SRS compared with upfront WBRT is ongoing.

The effect of chemotherapy on brain metastases is controversial. It is difficult to conduct clinical trials because most of the patients receive radiotherapy, and the chemotherapeutic agents that would be chosen are commonly used for the primary cancers. Although most brain metastases are considered to be chemoresistant because of the presence of the blood-brain barrier, they sometimes shrink with only the chemotherapy used for the treatment of the primary cancer. Chemotherapy could be an important treatment modality, particularly for recurrent brain metastases after radiotherapy.

No standard therapy for brain metastases has been established yet. Surgical removal is necessary for large tumors, but only a few patients have a chance of undergoing surgery, because of tumor multiplicity and poor performance status. WBRT, SRS, and chemotherapy should be used appropriately to obtain long survival and maintain a good quality of life for the patients. The cooperation of neurosurgeons, oncologists, nursing staff, social workers, and the patient's family is essential for the optimal treatment of metastatic brain tumors.

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REVIEW ARTICLE

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Strategy of surgery and radiation therapy for brain metastases

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Abstract Cancer patients with brain metastases have poor prognoses and their median survival time is about 1 year. Surgery with whole-brain radiation therapy (WBRT) has been used in the treatment of single brain metastasis measuring 3 cm or more. Stereotactic radiosurgery (SRS) including the use of the Gamma knife and Cyberknife is widely used for the treatment of small and multiple brain metastases; however, recent clinical studies have revealed that SRS + WBRT is superior to WBRT or SRS alone in terms of survival time and local tumor control rates. Here, surgical indications and the strategy of surgery and radiation therapy are discussed, based on many clinical trials of treatments for brain metastases. To improve the survival rate and quality of life for these cancer patients with brain metastases, it is necessary to choose the most suitable mode of surgery and radiotherapy with the close cooperation of physicians, surgeons, radiologists, and neurosurgeons, based on accumulated evidence.

Key words Brain metastases · Surgery · WBRT · SRS

Introduction

As cancer treatment has advanced, the survival of cancer patients has been prolonged, and the number of patients who have concomitant brain metastases has been increasing. According to the 11th edition of the Brain Tumor Registry of Japan,[1] the 1-year and 5-year survival rates of 4839 patients with brain metastases registered between 1991 and 1996 were 43.8% and 13.6%, respectively, whereas the corresponding rates for glioblastoma patients were 55.9% and 7.2%. The prognoses of patients with brain metastases and glioblastomas remain poor, showing similar treatment outcomes. Although various combinations of treatments, including surgery, whole-brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS) have been attempted, the median survival time (MST) of patients with brain metastases is about 1 year, because brain metastases is stage IV cancer and because their prognoses depend largely on the status of the primary focus. In Japan, there are currently about 50 gamma knife and 20 Cyberknife facilities that can easily provide SRS. Patients with multiple metastases or concomitant leptomeningeal metastases, for which WBRT is desirable, are also occasionally treated by SRS only. To improve the survival rate and quality of life (QOL) for these patients with brain metastases, it is necessary to choose the most suitable mode of surgery and radiotherapy, tailored to the individual needs of patients, based on accumulated evidence in different fields of medical practice (evidence-based medicine; EBM).

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Frequency of patients with brain metastases

According to the Metropolitan Detroit Cancer Surveillance System, brain metastases occurred in 9.6% of approximately 170000 patients diagnosed with cancer from 1973 to 2001.[2] In regard to the primary lesion, the incidence of brain metastases is reportedly 19.9% for lung cancer, 6.9% for melanoma, 6.5% for renal cancer, 5.1% for breast cancer, and 1.8% for colon cancer. A Dutch cohort study (2700 patients) found the incidence of brain metastases over 5 years to be 8.5%, and the incidences by primary lesion site were 16.3% for lung cancer, 7.4% for melanoma, 9.8% for renal cancer, 5.0% for breast cancer, and 1.2% for colon cancer.[3] Thus, approximately 10% of patients who had cancer developed brain metastases. According to Health and Welfare Statistics in Japan, there were 569000 patients with malignant neoplasms in 2001, and it is estimated that more than 50000 develop brain metastases annually. An analysis of autopsy cases revealed a higher frequency of brain metastases; brain metastases were found in 20%–40% of autopsied cancer patients.[4] The number of deaths from malignant neoplasms was approximately 336000 in 2007,

suggesting that there were 60000–120000 patients with brain metastases.[5] The cause of death in cancer patients with brain metastases was reported to be exacerbation of the primary lesion in 50%, and neural death due to brain metastases or leptomeningeal metastases in 30%,[6] suggesting that more than 20000 cases of neural death due to metastatic tumors occur in Japan annually. Considering that the number of annual deaths from primary malignant brain tumors, including glioma, in Japan is approximately 2000, controlling brain metastases is an important goal for neurosurgeons.

According to the 11th edition of the Brain Tumor Registry of Japan[1] based on collected data from mainly neurosurgical facilities, the frequencies of the primary foci in 10071 cancer patients with brain metastases registered between 1984 and 1996 were 52.3% for lung cancer, the highest, followed by breast (8.9%), renal (5.4%), rectal (5.2%), gastric (5.2%), colon (4.1%), head and neck (3.5%), hepatic (2.1%), uterine (1.7%), and thyroid (1.4%) cancers. Pathologically, adenocarcinoma was most frequent, accounting for 58.5%, whereas the frequency of squamous cell carcinoma was 13.5%.

The chief complaints of patients with brain metastases are focal signs including hemiparesis and aphasia (58%), signs of increased intracranial pressure (19%), and complaints without neurological symptoms (10%). Three percent of patients were asymptomatic and those patients were diagnosed by radiological findings.[1]

Prognostic factors

A Radiation Therapy Oncology Group (RTOG) study reviewed about 1200 patients enrolled in clinical trials that used WBRT, and analyzed prognostic factors by recursive-partitioning analysis (RPA) to classify them into RPA classes I-III.[7] Favorable prognostic factors for patients with metastatic brain tumor were Karnofsky performance status (KPS) of 70 or more, no distant metastasis other than brain metastases, controlled primary focus, and age less than 65 years; patients with these factors were considered to represent RPA class I (accounting for 20% of all subjects). KPS less than 70 was a poor prognostic factor, and such patients were categorized as RPA class III (accounting for 15%), whereas other factors were considered to represent RPA class II (accounting for 65%). MSTs were 7.1, 4.2, and 2.3 months for patients in RPA classes I, II, and III, respectively (Table 1). These RPA classes are commonly used when assessing treatment results for brain metastases.

Indications for surgery

Patients with brain metastases often have rapidly progressing neurologic symptoms, necessitating rapid determination of optimal therapeutic strategies. Figure 1 shows the therapeutic strategies used at the National Cancer Center in Japan.

Patients with a single metastasis measuring 3 cm or more, those with smaller tumors such as cerebellar neoplasms associated with severe neurologic symptoms due to cerebral edema, or those with multiple tumors with advanced neurologic symptoms in whom prompt improvement of neurologic symptoms is expected from surgery, undergo

Table 1. RPA classification and prognoses (MST) of cancer patients with brain metastases

Class I	KPS ≧70, age <64 years Controlled primary tumor No extracranial metastases
Class II	KPS ≧70 but other than class I
Class III	KPS <70

	n	Class I MST (months)	Class II MST (months)	Class III MST (months)
WBRT[7]	1176	7.1	4.2	2.3
SRS[16]	265	14.0	8.2	5.3
WBRT + SRS[16]	295	15.2	7.0	5.5
OPE + WBRT[10]	125	14.8	9.9	6.0

RPA, Recursive partitioning analysis; KPS, Karnofsky performance status; MST, median survival time; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; OPE, operation

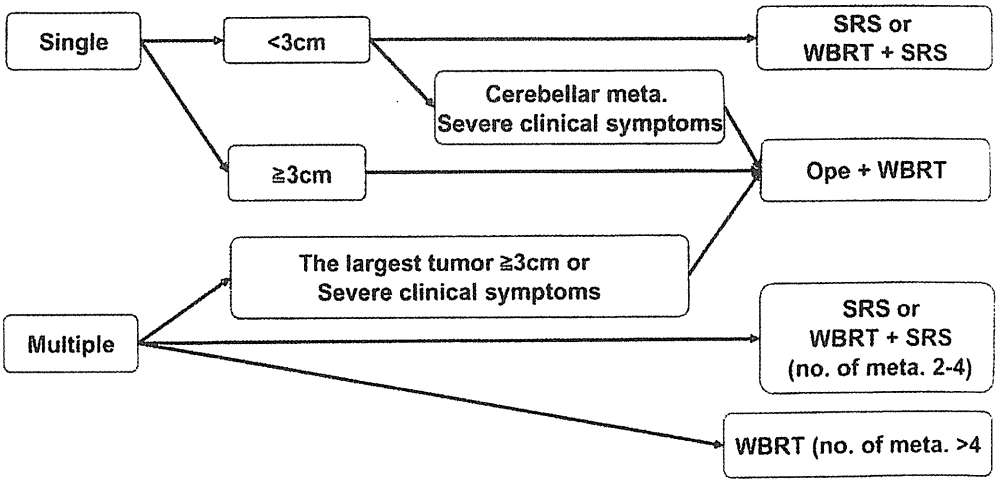

Fig. 1. Surgical and radiotherapy treatment of brain metastases (*meta*). *SRS*, Stereotactic radiosurgery; *WBRT*, whole-brain radiation therapy; *ope*, operation

craniotomy for tumor resection within 1 week of diagnosis and WBRT beginning 8 days after surgery, if possible. MST after WBRT without surgery is approximately 6 months, and therefore surgical candidates have a vital prognosis of at least 6 months. Considering that the MST of patients with brain metastases is approximately 1 year, it is critical to prevent worsening of neurologic symptoms and performance status (PS) in patients undergoing surgery.

Patients who have large cystic lesions in the eloquent area and those with poor PS or poor prognoses who are not good candidates for craniotomy for tumor resection under general anesthesia may undergo palliative insertion of an Ommaya reservoir for cystic tumor management. Removing the fluid content via the Ommaya reservoir to reduce the cyst prior to radiotherapy may effectively alleviate neurologic symptoms. Patients with a metastasis to the mesencephalic aqueduct, brainstem, or cerebellum, and those with obstructed cerebrospinal fluid (CSF) absorption resulting from carcinomatous meningitis may develop acute hydrocephalus. In these patients, endoscopic third ventriculostomy or ventriculoperitoneal shunt may ameliorate impaired consciousness.

Radiotherapy following surgery

According to the Brain Tumor Registry of Japan,[1] among 3793 patients with lung cancer who underwent surgery between 1981 and 1996, radiotherapy was added to the treatment protocol in 41.5%, whereas surgery alone was employed in 58.5%. Although surgery alone is a common therapeutic option in Japan, the 1-year survival rate was 50.9% for surgery combined with radiotherapy and 38.7% for surgery alone, showing better outcomes with the former treatment modality. Because approximately half of the patients undergoing surgery alone subsequently suffer recurrence,[8] the addition of radiotherapy is necessary. In patients with brain metastases, surgery combined with WBRT is the standard treatment worldwide. This strategy is based on the following findings. Patchell et al.[8] carried out a randomized controlled trial (RCT) of surgery + WBRT (36 Gy/12 fractions) vs surgery alone in patients with a single metastasis, and found that the MST was 10 months in the surgery + WBRT group and 3.75 months in the surgery-alone group. The local recurrence rates were 20% and 52%, respectively, and postoperative KPS was also more favorable in the surgery + WBRT arm. Similarly, Vecht et al.[9] reported that surgery combined with WBRT prolonged survival. On the other hand, a randomized study comparing surgery + WBRT (50.4 Gy) to surgery alone showed both local recurrence (10% vs 46%, respectively) and recurrence at other sites (14% vs 37%, respectively) to be significantly less frequent in patients given surgery + WBRT, although there was no significant intergroup difference in MST.[8] Based on the results of these RCTs, surgery combined with WBRT has become the standard treatment for a single brain metastasis. Agboola et al.[10] reported that MSTs with surgery + WBRT were 14.8, 9.9, and 6.0 months for patients in RPA classes I, II, and III (Table 1).

In Japan, postoperative local irradiation has commonly been applied to the site of tumor resection at various facilities. Indeed, until 2002, the National Cancer Center also employed focal radiation therapy (FRT) at 50 Gy in patients with a single tumor. However, there have been no RCTs comparing FRT and WBRT as modes of postoperative radiotherapy. At present, in consultation with radiologists and medical oncologists regarding the optimal postoperative radiotherapy, WBRT at 37.5 Gy (15 fractions/3 weeks) is generally used for patients in RTOG RPA class I postoperatively. In patients in RTOG RPA class II or III who have a poor prognosis due to their general condition, WBRT at 30 Gy (10 fractions/2 weeks) is applied, with the goal of an early return home if possible. An analysis of the mode of recurrence in 109 patients who underwent FRT at 50 Gy ($n = 58$) or WBRT at 30 Gy ($n = 51$) postoperatively at the National Cancer Center demonstrated the absence of recurrence in 43% and 59% of patients given FRT and WBRT, respectively. Thus, recurrence was less frequent in patients given WBRT than in those given FRT. The rates of recurrence at the site of surgery were 12% and 14%, respectively, showing no marked difference. However, recurrence in areas other than the surgical site was slightly more frequent after FRT (33%) than after WBRT (12%). Metastases to the spinal cord occurred in 3% and 4% of patients given FRT or WBRT, respectively, and the incidences of carcinomatous meningitis were 9% and 12%, respectively, showing no marked differences in dissemination of tumors between the two groups.

In 180 patients who underwent craniotomy for tumor resection combined with radiotherapy between 1990 and 2005 in the Neurosurgery Division at the National Cancer Center, MST was 12.3 months. In 47 patients with pulmonary adenocarcinoma, MST was 15.1 months, and the 5-year survival rate was 15.0%. MST and the 5-year survival rate in 18 patients with squamous cell carcinoma of the lung were 14.9 months and 23.2%, respectively, while the corresponding figures were 13.8 months and 32.5%, respectively, in 29 patients with breast cancer.

Surgical complications

The most important issue in the surgical treatment of brain metastases is to avoid deterioration of PS. Even if there is only a possibility that paralysis may be ameliorated by long-term rehabilitation training, partial resection should be employed rather than risking the exacerbation of paralysis due to total resection, and radiotherapy should be used to address possible residual tumor, given its anticipated efficacy.

Paek et al.,[11] who reviewed 208 patients treated surgically, reported that 1.9% died within 30 days, and that postoperative neurologic deterioration occurred in 6%. Systemic complications, including pneumonia, urinary infection, and venous thrombosis occurred in 13.9% of the patients.

In a series of 152 patients who underwent craniotomy for tumor resection between 2000 and 2006 at the National Cancer Center, complications occurred in 6 (3.9%). Exacerbation of paralysis occurred in 2 patients (1.3%) due to postoperative hematoma and in 1 (0.7%) due to tumor resection. One patient (0.7%) developed a surgical wound infection and another, spinal fluid leakage. Sudden cardiopulmonary arrest following suboccipital craniotomy occurred in 1 patient with a cerebellar metastasis from lung cancer. It was speculated that the cardiopulmonary arrest in this patient was attributable to circulatory volume loss due to the use of mannitol at the time of craniotomy, as the patient had had severe intracranial hypertension preoperatively and dehydration had been exacerbated by mannitol or glycerol before surgery. This patient was successfully resuscitated and craniotomy was performed again 1 week later, with successful tumor resection; the patient was discharged without neurologic abnormalities. This case provided a warning regarding the risk of mannitol use in dehydrated patients. There was one death (0.7%) within 30 postoperative days. This patient was elderly (80 years) and was found to have concomitant carcinomatous meningitis at autopsy.

Radiotherapy for patients not suitable for surgery

WBRT is the standard radiotherapy for patients who are not good candidates for surgery, usually with a radiation dose of 30 Gy (3 Gy × 10 fractions/2 weeks). This procedure is reported to exert a therapeutic effect equal to WBRT at 40 Gy (2 Gy × 20 fractions).[12] WBRT at 30 Gy has been widely employed because it requires only a short treatment period. However, irradiation at 37.5 Gy using a lower dose for each fraction (2.5 Gy × 15 fractions/3 weeks) has also been used in many clinical studies, conducted after the RTOG 9508 study, to reduce adverse reactions to irradiation. On the other hand, reported adverse reactions to WBRT include leukoencephalopathy and progressive dementia, ataxia, and incontinence due to radiation-induced necrosis, occurring in approximately 10% of patients.[13,14] SRS using Lekshell Gamma knife (Elekta; Stockholm, Sweden), Cyberknife (Accuray; Sunnyvale, CA, USA), X-knife (Radionics; Burlington, VT, USA), or Linear accelerator (Linac) (Elekta; Stockholm, Sweden) radiosurgery is also useful for treating tumors with diameters of 3 cm or less. In Japan, SRS alone is widely used for single lesions. Serizawa et al.[15] reported that an MST of 9.0 months was achieved in 521 patients who underwent gamma knife radiosurgery. Sneed et al.,[16] reported that MSTs with SRS alone were 14.0, 8.2, and 5.3 months for patients in RPA classes I, II, and III (Table 1).

Although there has been no RCT comparing SRS and WBRT, the Japanese Radiation Oncology Study Group (JROSG) carried out an RCT in patients who had four or fewer brain metastases measuring 3 cm or less to compare WBRT + SRS (65 patients) and SRS alone (67 patients).[17] The 1-year survival rate and MST were 38.5% and 7.5 months, respectively, in the WBRT + SRS group, and 28.4% and 8.0 months, respectively, in the SRS-alone group, respectively, showing no marked differences between the two groups. The frequencies of neural death due to brain metastases were 19.3% and 22.8%, respectively. The respective incidences of new lesions at 1 year and the rates of recurrence of brain metastases, including local recurrence, were 41.5% and 46.8% in the WBRT + SRS group, and 63.7% and 76.4% in the SRS-alone group, demonstrating significantly lower rates with the combination of WBRT and SRS. Additional stereotactic irradiation was required in 10 patients in the combined treatment group and 29 in the SRS-alone group. However, additional stereotactic irradiation was actually performed in 9 and 19 patients, respectively; salvage therapy could not be conducted in all patients with tumor recurrence. The mean memory test score (maximum score, 30 points) on the mini-mental state examination (MMSE) in patients who survived for more than 1 year was 27.0 (range, 23–30) in the combined group and 28.0 (range, 18–30) in the SRS-alone group, showing no significant difference between the two groups. Thus, SRS combined with WBRT did not increase the incidence of dementia as compared with SRS alone. In the randomized RTOG 9508 study, patients who had three or fewer metastatic foci measuring 4 cm or less in greatest dimension underwent WBRT (37.5 Gy/15 fractions) combined with SRS (164 patients, including 92 patients with a single tumor) or WBRT alone (167 patients, including 94 patients with a single tumor).[6] Among those with a single metastasis, MST was 6.5 months in the WBRT + SRS group and 4.9 months in the WBRT-alone group, showing a significant intergroup difference (P = 0.039). KPS at 6 months was well maintained or improved in 43% and 27% of the patients in the WBRT + SRS and WBRT-alone groups, respectively, showing significantly better results for the combined irradiation group. The response rate at 3 months and the local control rate at 1 year were also superior in the combined irradiation group, indicating the usefulness of additional SRS in patients with a single tumor. In patients with two to three metastatic foci, MST was 5.8 months after combined irradiation and 6.7 months after WBRT alone, showing no significant difference.

Based on the results of various prior clinical studies, WBRT combined with SRS might be considered to be a feasible standard treatment for a single metastasis.[16,18] However, in Japan, gamma knife radiosurgery alone is often used to treat patients with three to four lesions measuring 3 cm or less in diameter. On the other hand, when medical oncologists describe the above evidence to patients, an increasing number of patients choose gamma knife treatment after WBRT.

In patients with many (five or more) lesions and those who have concomitant leptomeningeal metastases, there is no evidence supporting the propriety of SRS treatment alone, and WBRT is therefore necessary.

When considering the mode of radiotherapy for brain metastases, it is necessary to look at clinical trials that use neurocognitive function as an endpoint, in addition to the survival period and the recurrence rate. There may be

future alterations in the standard treatment, as further evidence is accumulated.

Clinical studies of brain metastases in Japan

Although SRS is associated with more frequent recurrence in untreated areas than WBRT, it is advantageous in that the treatment time is shorter and anorexia and general malaise are mild, in contrast to symptoms seen during or immediately after WBRT. The efficacy of SRS, however, lacks corroborative evidence, in contrast to WBRT, as discussed above. Many patients, however, express concern about irradiation applied to normal brain tissue, believing that it induces progressive dementia. In this regard, the Japan Clinical Oncology Group (JCOG)-Brain Tumor Group started an RCT in 2006 to compare the efficacies of surgery combined with WBRT and surgery combined with additional salvage radiation therapy with SRS for residual tumors in patients with four or fewer brain metastases, using the overall survival period, incidence of dementia (proportion of patients showing worsening of MMSE results), and maintained QOL (proportion of patients with no deterioration of PS) as endpoints. This is a noninferiority study. If it is demonstrated that the test treatment (surgery + additional SRS) is not inferior to the standard treatment (surgery + WBRT) in terms of overall survival, the test treatment is regarded as being more useful. As noted above, WBRT combined with SRS is considered to be the standard treatment for patients suitable for SRS. The actual situation is that SRS alone, performed with a gamma knife or other systems, is employed without careful consideration, for fear of adverse reactions to WBRT. The above JCOG trial and various other clinical investigations, seeking to reduce adverse events and to enhance the efficacy of irradiation, are ongoing.

Recurrence after surgery and radiotherapy

There is no standard treatment for recurrence after surgery combined with WBRT or after radiotherapy. Patients undergo magnetic resonance imaging (MRI) studies every 2–3 months after treatment, and if recurrence is detected, surgery or SRS with a gamma knife will be performed. The therapeutic outcomes of operable patients are not necessarily poor. In patients with recurrence, MST after the second surgery is reportedly 11.5 months,[19] whereas MST after surgery in patients with recurrence after gamma knife radiosurgery is 11.1 months.[20] In a study reported before 1990, when additional gamma knife treatment was not available, patients with recurrences after WBRT at 30 Gy received another WBRT at 25 Gy. Therapeutic efficacy was achieved in 42% of these patients, and MST was 5 months, although there was no detailed discussion of safety.[21]

It is unclear whether these post-treatments achieve better survival or better QOL. The most suitable treatment should be chosen for recurrent cases, based on the patient's general condition, neurologic symptoms, and prognosis.

Leptomeningeal metastases or carcinomatous meningitis

In patients diagnosed with leptomeningeal metastases, MST is 3–6 months.[22] Intrathecal administration of methotrexate (MTX) or cytarabine (Ara-C) is a common treatment strategy. Ommaya reservoir insertion is often employed under local anesthesia to reduce the burden on the patient during lumbar puncture and to achieve intraventricular drug administration. Among the complications of this procedure, rates of extraventricular insertion, postoperative infection, and postoperative bleeding[23] are reportedly 3%–12%, 2%–9% and 1%–3%, respectively. Because postoperative deaths have also been reported, caution is required in selecting this procedure. In our hospital, patients with suspected leptomeningeal metastases undergo lumbar puncture and CSF cytology. Once a definitive diagnosis has been obtained, MTX is given intrathecally by lumbar puncture. When the CSF cell count decreases in response to intrathecal MTX, Ommaya reservoir insertion is carried out to allow intraventricular MTX administration. In patients with neurologic symptoms but no prior radiotherapy, WBRT is added. However, the MST of patients (n = 22) treated with MTX via an inserted Ommaya reservoir at our hospital was only 4 months, a poor outcome.

Use of steroids and anticonvulsants

When using steroids for cerebral edema due to brain metastases, attention should be paid to possible adverse reactions such as gastrointestinal bleeding, hyperglycemia, peripheral edema, mental symptoms including a depressive state and insomnia, osteoporosis, and infectious diseases including oral candidiasis.[24] In patients with paralysis, attention to pulmonary embolism due to deep venous thrombosis (DVT) is necessary. If DVT is suspected, the patient should undergo pelvic computed tomography (CT) and ultrasonography, and prophylactic treatment such as warfarinization or inferior vena cava filter placement should be administered.

Pneumonia resulting from decreased immunocompetence due to steroid therapy is common. It should be kept in mind that *Pneumocystis carinii* pneumonia (PCP) may occur in patients on prolonged steroid therapy or in those of advanced age. Patients treated at our hospital who developed PCP, presumably because of prolonged steroid therapy for malignant glioma, had received the equivalent of 15 mg or more prednisolone. From this experience, we have found that trimethoprim-sulfamethoxazole is effective prophylaxis for PCP.

Convulsive seizures occur in 20%–40% of patients with brain tumors, and it may be surprising that there is as yet no evidence showing a prophylactic effect of antiepileptic drugs on these seizures. In a study of valproic acid and placebo administration in patients with brain tumors (90% had brain metastases) with no history of convulsive seizures,[25] 35% and 24%, respectively, developed convulsions during the mean observation period of 7 months, indicating

that valproic acid exerted no prophylactic effect. The American Academy of Neurology (AAN) reviewed 12 previous studies and concluded that there was no distinct prophylactic effect of antiepileptic drugs on convulsive seizures. Thus, the AAN does not recommend regular administration of antiepileptic drugs to patients who have no history of convulsive seizures.[26]

Phenytoin, phenobarbital, and carbamazepine activate the hepatic enzyme cytochrome P450, thereby enhancing the metabolism of various concomitantly used molecular-targeting drugs and anticancer drugs such as nitrosourea (ACNU), MTX, irinotecan (CPT), and adriamycin (ADM), consequently lowering their blood concentrations. Thus, caution is necessary in continuing systemic chemotherapy.[27] In patients who have convulsive seizures and those at high risk for such seizures because of multiple lesions and other factors, medication should begin with a drug that does not activate P450 (e.g., valproic acid or zonisamide), but caution is necessary, as the anticonvulsant drug itself can cause bone marrow suppression.

Conclusions

MST in patients with brain metastases is only about 1 year. In the treatment of brain metastases, it is necessary to maintain the patient's QOL and activities of daily living. For this purpose, the therapeutic strategy should be decided with the close cooperation of internists, surgeons, radiologists, and neurosurgeons, taking into account the patient's clinical history, PS, neurologic findings, tumor size, number of lesions, control of the primary focus, and prognosis.

Conflict of interest

No author has any conflict of interest.

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ORIGINAL ARTICLE

Quality assurance of volumetric modulated arc therapy using Elekta Synergy

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Abstract

Purpose. Recently, Elekta has supplied volumetric modulated arc therapy (VMAT) in which multi-leaf collimator (MLC) shape, jaw position, collimator angle, and gantry speed vary continuously during gantry rotation. A quality assurance procedure for VMAT delivery is described. *Methods and materials.* A single-arc VMAT plan with 73 control points (CPs) and 5-degree gantry angle spacing for a prostate cancer patient has been created by ERGO++ treatment planning system (TPS), where MLC shapes are given by anatomic relationship between a target and organs at risk and the monitor unit for each CP is optimized based on given dose prescriptions. Actual leaf and jaw positions, gantry angles and dose rates during prostate VMAT delivery were recorded in every 0.25 seconds, and the errors between planned and actual values were evaluated. The dose re-calculation using these recorded data has been performed and compared with the original TPS plan using the gamma index. *Results.* Typical peak errors of gantry angles, leaf positions, and jaw positions were 3 degrees, 0.6 mm, and 1 mm, respectively. The dose distribution obtained by the TPS plan and the recalculated one agreed well under 2%-2 mm gamma index criteria. *Conclusions.* Quality assurance for prostate VMAT delivery has been performed with a satisfied result.

The concept of volumetric modulated arc therapy (VMAT) originated from the conformal avoidance radiation therapy [1] with a dynamical movement of MLC while rotating the gantry. By modulating beam intensity during the gantry rotation, intensity modulated arc therapy (IMAT) was proposed and further investigated [2–6]. VMAT is one of the techniques to realize IMAT by varying gantry speed and dose rate with dynamical movement of MLC and jaw [7]. Recently, this has been clinically available [8–10] and a combination of Elekta Synergy with the latest linac control software and ERGO++ treatment planning system (TPS) is one example.

The purpose of this paper is to investigate how much error is caused in dose distribution due to the fluctuation in the dynamical parameters. The linac controller in Elekta Synergy (Elekta, Crawley, UK), RT Desktop 7.0.1, serves to record measured data of dose rates, gantry angles, MLC and jaw positions with 0.25 s interval during VMAT treatment. We can evaluate the influence of these errors by recalculating the dose distribution with these actual dynamical parameters. Since this is an independent simulation analysis and therefore we may be able to specify the cause when VMAT film verification failed.

Methods and materials

A single-arc VMAT plan for prostate cancer was created by ERGO++ v1.71 TPS (Elekta/3DLine, Milano) with D95 prescription (dose to 95% of target volume) of 76 Gy in 38 fractions. A single arc was discretized into 73 static beams or CPs placed at 5-degree gantry angle intervals between −175 and +175 degrees and the first and last CPs were positioned at −179 and +179 degrees (Figure 1). The field shape for each control point was determined by either conformal or conformal avoidance strategy with a 6 mm leaf margin to Planning Target Volume (PTV). In other words, the rectum was

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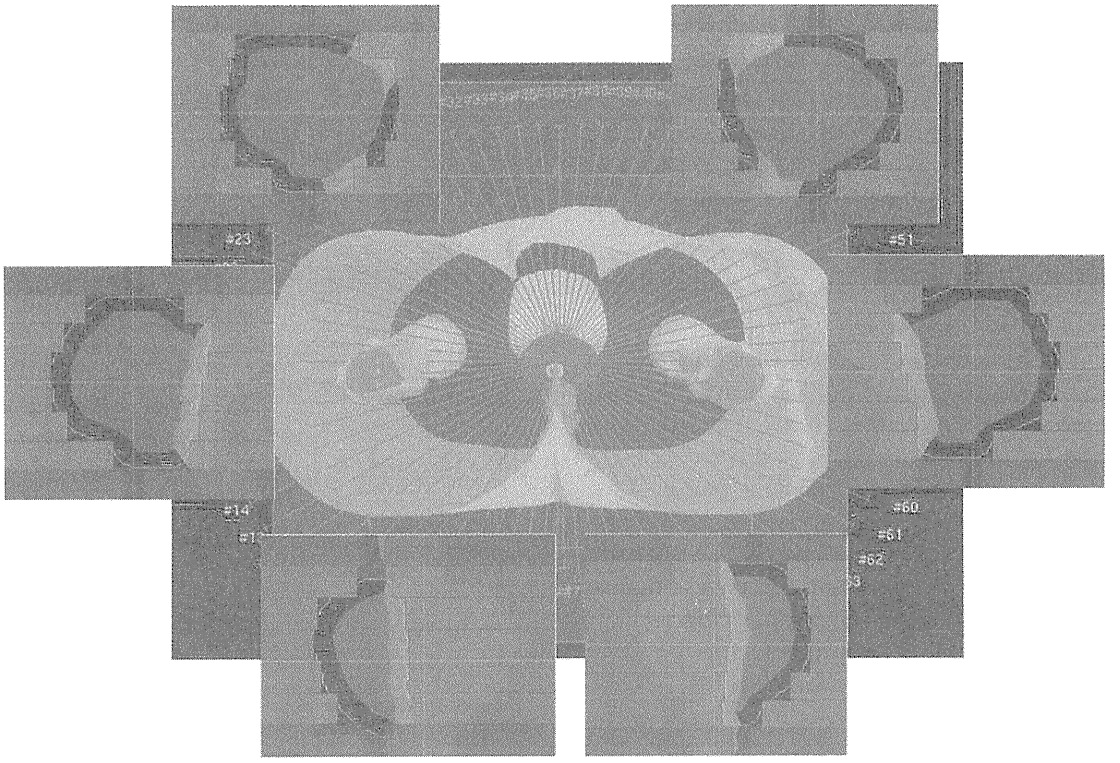

Figure 1. A single-arc VMAT plan with 73 CPs and 5-degree gantry angle spacing for a prostate cancer patient has been created by ERGO++ treatment planning system, where MLC shapes are given by anatomies of target and organs at risk and monitor units for each CP is optimized by simulated annealing algorithm based on given dose prescriptions. The red and pink regions are PTV and rectum, respectively.

partially shielded by MLC when it was in front of the target in beam's eye view, while the whole target was irradiated when it was in front of the rectum.

In the present study, the collimator angle was fixed at 180 degrees. Beam weights for all CPs were optimized by inverse planning based on the simulated annealing algorithm. Dose grid resolution was 2 mm × 2 mm × 2 mm for 3D calculation. After inverse planning, the CPs were grouped into a single arc with the VMAT sequencer in ERGO++ TPS, where a monitor unit (MU) to be delivered between two adjacent CPs was calculated by adding MUs at the two adjacent CPs and then multiplied by 0.5. The created plan was sent to MOSAIQ v1.6 (Elekta IMPAC, USA), and then delivered by the RT desktop controller.

For dose verification, VMAT plan was transferred to two phantom studies. One was a cylindrical water phantom with 0.015 cc pin-point ionization chamber (Type 31014, PTW, Germany) placed at the isocentre. The other was a pelvic water phantom including a GafChromic film (International Specialty Products, NJ, USA) to measure the dose distribution on axial, coronal, and sagittal planes including the isocentre. The GafChromic film was scanned using a flatbed scanner (EPSON GT-X770, Japan) and the gamma index with 3% of a dose at the measurement point and 3 mm has been evaluated by using DD-system v9.0 (R-tech, Japan).

The linac controller in service mode was capable of recording the actual gantry angle, MLC and jaw positions, and dose rate as a function of time. The MLC and jaw positions in each CP computed by ERGO++ were compared with the corresponding measured values. The cumulative MU error is practically negligible because Elekta VMAT delivery is based on MU-based servo control. Instead, the gantry angle error is discussed, which is defined as the difference between the gantry angle for each CP and the gantry angle where a cumulative MU reaches a specified value. A gantry speed dependence of these errors with the same VMAT plan was also examined by employing two times slower gantry speed than a commonly used clinical speed.

Using the actual data of gantry angle, MLC and jaw positions, and the cumulative MUs, dose distribution was re-calculated using Pinnacle v7.4i TPS (Philips, USA), and the dose in the original plan transferred into Pinnacle was compared with the re-calculated dose distribution.

Results

The beam-on time was typically 100 s for a single-arc prostate VMAT delivery. The isocentre dose discrepancy between plans and measurements for 17 patients was $-0.5 \pm 0.8\%$ (s.d.). The averages of the pass rate with a gamma criteria of 3 mm and 3% of a dose at the measurement point were 97.3%, 91.8%, and 92.2% on axial, sagittal, and coronal planes for a region having a dose greater than 30% of the isocentre dose, respectively.

Figure 2 demonstrates measured errors between planned and actual gantry angles during VMAT delivery for three consecutive runs. The red data points show the position errors for a normal delivery time of 100 s, whereas the blue data points show those for a delivery time of 200 s. The bar shows the error range for the three runs. The gantry angle ranges of zero gantry angle error were due to move-only control points with no dose delivery.

Figure 3a and b show measured errors between planned and actual leaf positions during VMAT delivery for three consecutive runs of the same VMAT plan as in Figure 2. Figure 3a depicts a position error of right leaf number 20, which is one of the centre leaves, whereas Figure 3b depicts a position error of left leaf number 20. Again the red data points show the position errors for a normal delivery time of 100 s, whereas the blue data points show those for a delivery time of 200 s. The bar shows the error range for the three runs. The gantry angle ranges of zero leaf error were due to move-only control points with no dose delivery.

Figure 4a and b depicts measured errors between planned and actual X1 and X2 back-up jaw positions, respectively, during VMAT delivery for three consecutive runs of the same VMAT plan. Once again, the red data points show the position errors for a normal delivery time of 100 s, whereas the blue data points show those for a delivery time of 200 s. The bar shows the error range for the three runs. The gantry angle ranges of zero back-up jaw error were due to move-only control points with no dose delivery.

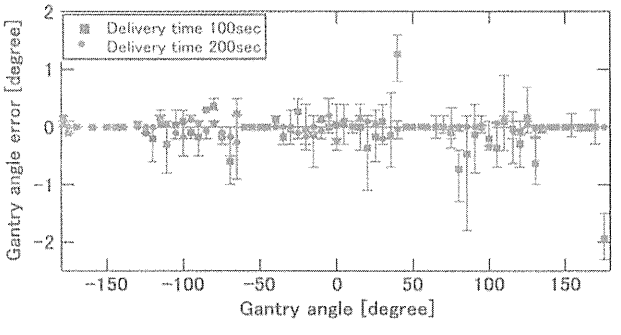

Figure 2. Measured errors between planned and actual gantry angles for three consecutive runs of the same VMAT plan. The red data points show the position errors for a normal delivery time of 100 s, whereas the blue data points show those for a delivery time of 200 s. The bar shows the error range for the three runs.

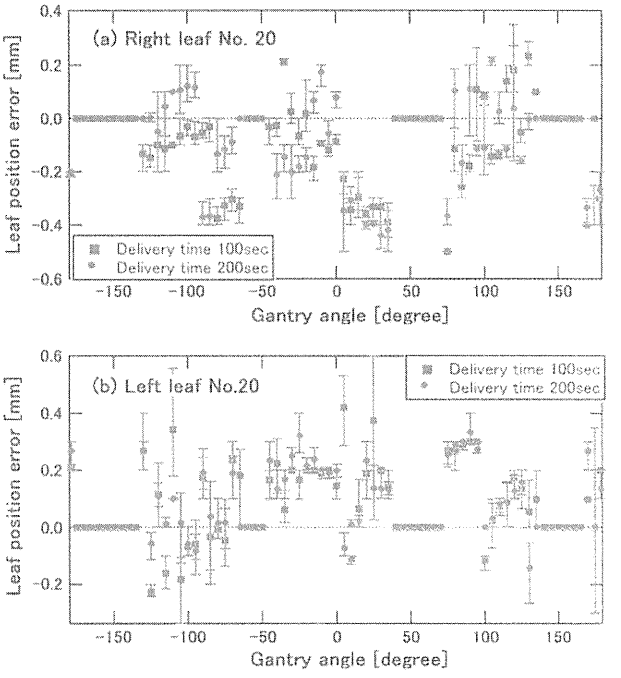

Figure 3. Measured errors between planned and actual leaf positions of the two centre leaves for three consecutive runs of the same VMAT plan: (a) position error of right leaf number 20, (b) position error of left leaf number 20. Again the red data points show the position errors for a normal delivery time of 100 s, whereas the blue data points show those for a delivery time of 200 s. The bar shows the error range for the three runs. The gantry angle ranges of zero leaf error were due to move-only control points with no dose delivery.

Figure 5a and b show gamma-index comparisons between an ERGO++ plan and re-calculated dose using actual data of MLC and jaw positions, gantry angles, and MUs with an interval of every 1 s. The red areas indicate gamma indices of larger than one under criteria of (a) 2% of a dose at the calculated point and 2 mm and (b) 1% of a dose at the calculated point and 1 mm.

Discussion

We have shown highly accurate prostate VMAT delivery using Elekta Synergy and ERGO++ TPS. While the dose agreement in the isocentre shows that total MU is correctly delivered, the agreement of dose distribution on axial, sagittal, and coronal planes assures accurate VMAT delivery. In the Synergy control system, the MLC, jaw, and gantry speed are servo-controlled based on cumulative MUs in each CP. Hence the errors in such dynamical parameters are quickly compensated by

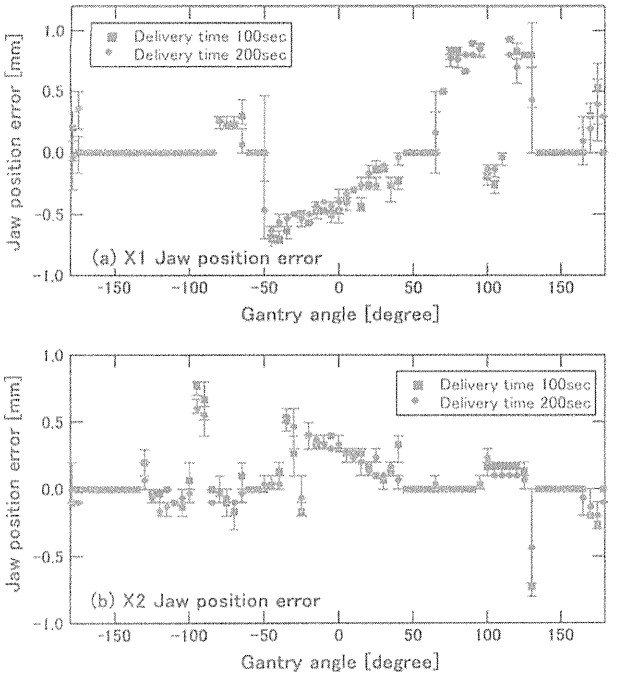

Figure 4. Measured errors between planned and actual back-up jaw positions for three consecutive runs of the same VMAT plan: (a) position error of X1 jaw, (b) position error of X2 jaw. Once again the red data points show the position errors for a normal delivery time of 100 s, whereas the blue data points show those for a delivery time of 200 s. The bar shows the error range for the three runs. The gantry angle ranges of zero back-up jaw error were due to move-only control points with no dose delivery.

real-time feedback control. For instance, it was found that the gantry angle error was immediately corrected as seen in Figure 2. In addition to the mechanical control, it is very important to mention that ERGO++ creates the MLC shape based on the anatomy relationship between the target and organs at risk from the beams eye view. Since it is a smooth function of gantry angle, no major changes are observed in MLC and jaw positions between adjacent control points thereby leading to more accurate dose calculation in TPS.

In the present work, the errors in gantry angles, MLC and jaw positions during VMAT delivery were analyzed. As seen in Figures 2–4, these errors were reproduced among three consecutive runs of the same VMAT plan, and were considered to be caused by accelerations of gantry, leaves, and jaws, which were required in almost the same gantry angles. In fact, it was clearly observed that the gantry angle error decreased when the gantry speed was slower as shown in Figure 2. In principle, smaller leaf and jaw position errors can be anticipated when the gantry speed is slower due to lower leaf and jaw speeds. In the present prostate plan which has no large leaf and jaw movements during gantry rotation, the leaf and back-up jaw position errors were comparable between two different delivery times. Instead, error tolerances of leaf and jaw positions given in the radiation control system may be a major cause of the observed errors.

As shown in Figure 5, the influence of these dynamical errors was negligible under criteria of 2% of a dose at the calculated point and 2 mm. Even under 1% of a dose at the calculated point and 1 mm criteria, the result was good except for low dose region. In other words, the errors in the dynamical parameters with the observed orders in prostate VMAT delivery do not affect the resulting dose distribution significantly.

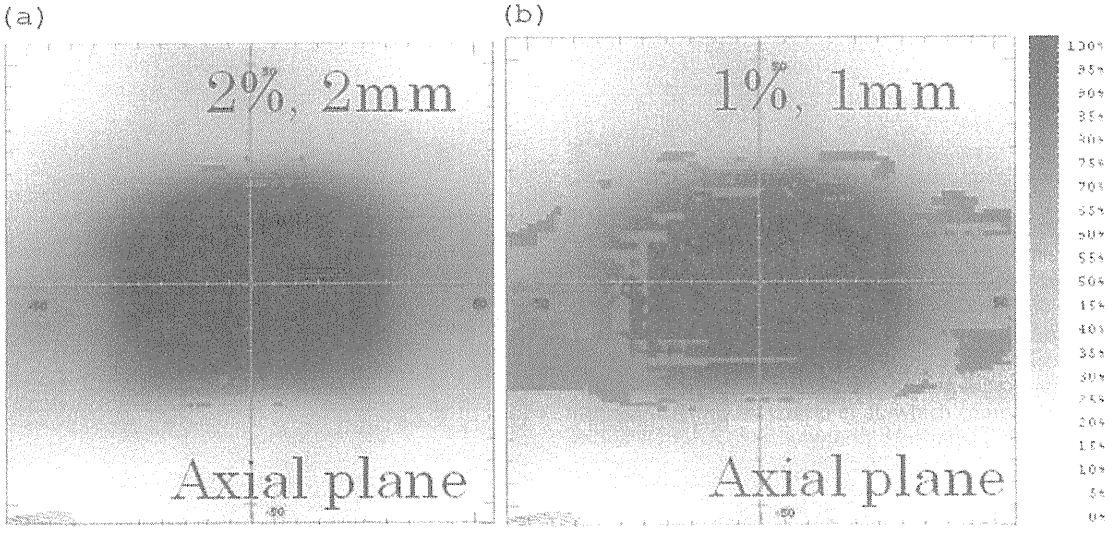

Figure 5. Gamma comparison between an ERGO++ plan and re-calculated dose using actual data of MLC and jaw positions, gantry angles, and MUs with an interval of every 1 s. The red areas indicate gamma indices of larger than one under criteria of (a) 2% of a dose at the calculated point and 2 mm and (b) 1% of a dose at the calculated point and 1 mm.

Conclusion

VMAT dose measurement for prostate cancer agreed well with the plan created by ERGO++. The observed errors of the dynamical parameter did not affect the dose distribution significantly. Quality assurance for prostate VMAT plans has been performed with a satisfied result.

Declaration of interest: Dr. Nakagawa receives research funding from Elekta KK.

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Lung cancer RT

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

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ABSTRACT

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

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

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

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

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

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

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

Methods and materials

Patients

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

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

Details of treatment

Radiotherapy

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

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

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

Chemotherapy

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

Evaluation

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

Table 1
Baseline patient characteristics.

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

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

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

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

Results

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

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

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

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

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

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

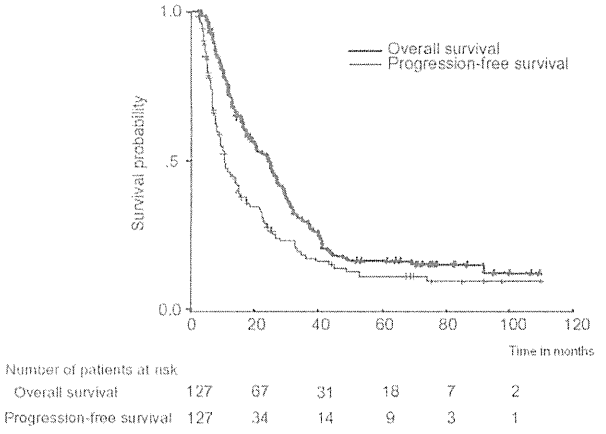

Fig. 1. Overall and progression-free survival curves of all the 127 patients. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Table 2
Details of all the first failures.

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

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

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

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

Discussion

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

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

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

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

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

Table 3
Patients with CTVs failure.

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

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

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

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

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

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

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

Conclusion

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

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