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.

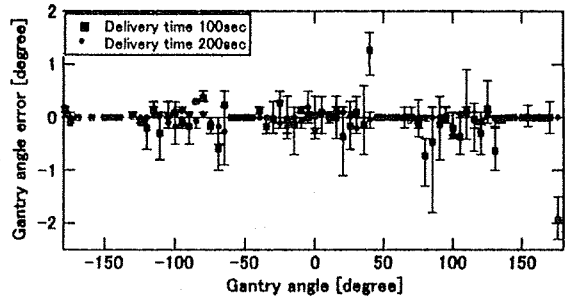

Figure 2. Measured errors between planned and actual gantry angles for three consecutive runs of the same VMAT plan. The red data points show the position errors for a normal delivery time of 100 s, whereas the blue data points show those for a delivery time of 200 s. The bar shows the error range for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

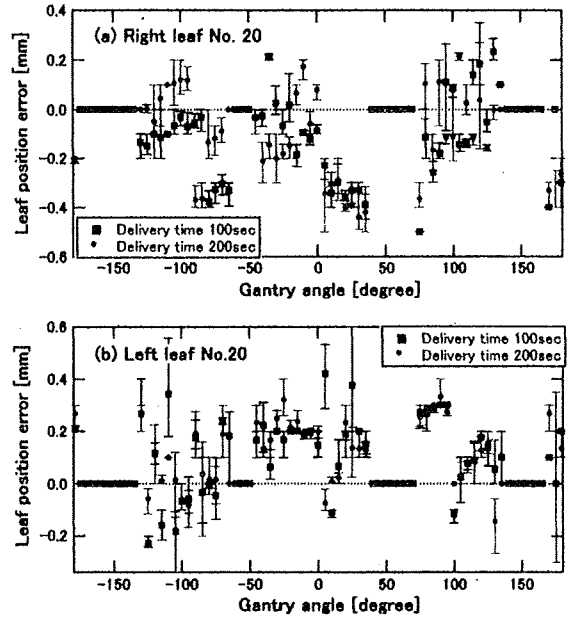

Figure 3. Measured errors between planned and actual leaf positions of the two centre leaves for three consecutive runs of the same VMAT plan: (a) position error of right leaf number 20, (b) position error of left leaf number 20. Again the red data points show the position errors for a normal delivery 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

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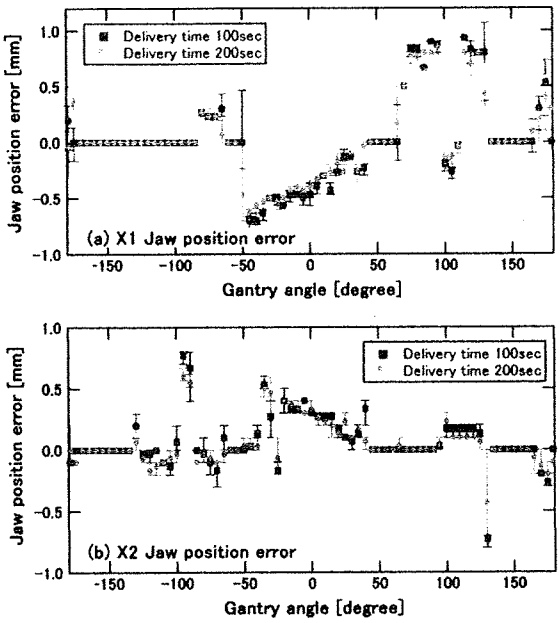

Figure 4. Measured errors between planned and actual back-up jaw positions for three consecutive runs of the same VMAT plan: (a) position error of X1 jaw, (b) position error of X2 jaw. Once again the red data points show the position errors for a normal delivery time of 100 s, whereas the blue data points 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.

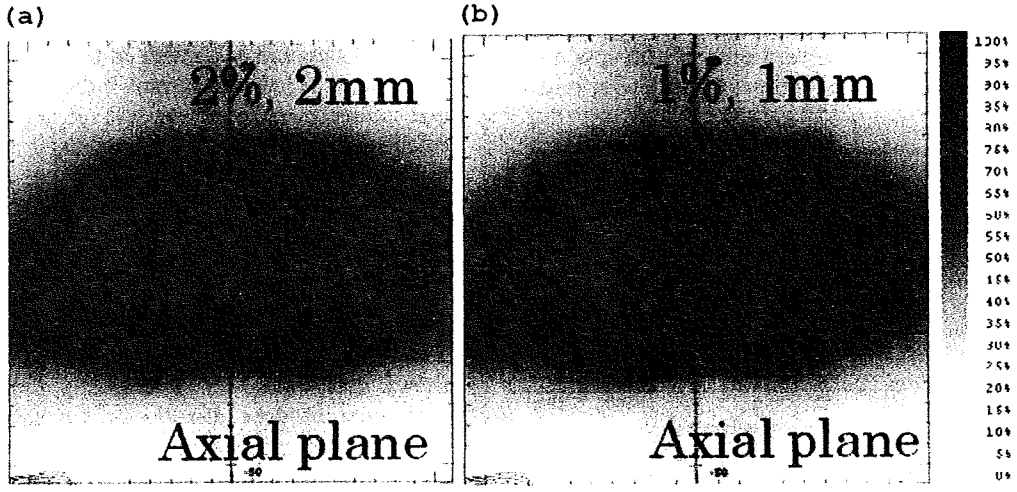

Figure 5. Gamma comparison between an ERGO++ plan and re-calculated dose using actual data of MLC and jaw positions, gantry angles, and MUs with an interval of every 1 s. The red areas indicate gamma indices of larger than one under criteria of (a) 2% of a dose at the calculated point and 2 mm and (b)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

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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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Stereotactic Radiosurgery for Skull Base Meningioma

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Abstract

Stereotactic radiosurgery is now a treatment option for meningiomas, especially for high-risk patients such as those with skull base lesions. The clinical outcomes were retrospectively analyzed of stereotactic radiosurgery using the Leksell Gamma Knife® performed for 98 patients with 106 skull base meningiomas at the University of Tokyo Hospital between June 1990 and April 2006 and followed up for more than a year. After a median follow-up period of 53.2 months (range 12.2–204.4 months), local tumor control rates were 86.9% and 78.9% at 5 years and 10 years, respectively. Tumors with volume of 4 cm^3 or smaller (97.5% vs. 76.1% at 5 years, p = 0.001) and tumors completely included within the isodose line of 14 Gy or more (97.5% vs. 67.2% at 5 years, p = 0.0006) had higher local control rates. Postoperative residual tumors treated by stereotactic radiosurgery were controlled in all 25 cases. Cranial nerve deficits were improved, stable, and deteriorated in 12, 64, and 3 patients, respectively, after stereotactic radiosurgery. Stereotactic radiosurgery was effective treatment method for local control of skull base meningiomas, especially for small or postoperative residual tumors. Correct combination of microsurgery and radiosurgery leads to excellent local control.

Key words: gamma knife, skull base, meningioma, stereotactic radiosurgery, local control

Introduction

Meningioma is the most common type of intracranial tumor arising from the meninges, with an incidence of 4.5 per 100,000 person-years, and accounts for 30.1% of all primary brain and central nervous system tumors.[3] The standard treatment for meningioma is surgical resection through craniotomy, targeted at gross total removal.[2,4,6,9,16,23,24,31,35] The treatment goal is long-term tumor control with minimal neurological morbidity. However, the tumor often extends to important neurovascular structures in the skull base, so total tumor resection (Simpson grades 1–2) is achieved in only 20–87.5% of patients.[2,4,23,24,31,35] Unacceptably high incidences of symptomatic recurrence are observed after subtotal resection of meningiomas.[20,33] In addition, postoperative complications occur in 16.1–61.5% of patients, although overall complication rates are not always reported.[2,23,31,35]

Stereotactic radiosurgery has now become a less invasive and effective treatment option for intracranial meningioma, especially in patients with high-risk tumors such as skull base lesions.[1,11–16,18,19,21,22,26,27,30,32,34,37] Stereotactic radiosurgery provides excellent outcomes with local tumor control rates of 85–100%, but these rates tend to fall with longer follow-up periods.[11–15,18,19,21,26,27,30,32,34] However, recent local tumor control rates have been nearly 100% for patients who had undergone Simpson grade 1 surgery.[16,28] Therefore, correct combination of microsurgery and radiosurgery would seem to have attained better clinical results with cavernous sinus meningiomas in our earlier series and in other institutions.[5,7,10,17,19,25] The Leksell Gamma Knife® (Elekta Instruments AB, Stockholm, Sweden) was installed in 1990 at the University of Tokyo Hospital. Since then, we have treated patients with intracranial tumors by stereotactic radiosurgery as a single modality treatment or in combination with surgery.

This study retrospectively reviewed the outcomes of stereotactic radiosurgery for skull base meningioma at the University of Tokyo Hospital and analyzed the factors affecting the results.

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Materials and Methods

Ninety-eight patients with 106 skull base meningiomas were treated by stereotactic radiosurgery, twice in 6 patients and three times in one patient, at the University of Tokyo Hospital and followed up for more than a year between June 1990 and April 2006. The clinical courses and treatment outcomes were retrospectively analyzed (Table 1).

Written informed consent was obtained from the patients before treatment. The patients were immobilized with a Leksell stereotactic coordinating frame and underwent high-resolution stereotactic magnetic resonance (MR) imaging or computed tomography (CT). The treatment plan was based on the stereotactic images processed with commercially available software (KULA or GammaPlan; Elekta Instruments AB). The tumor was generally covered with the 40–50% isodose line, and the designated treatment dose (ideally 14 to 18 Gy) was delivered to the tumor margin.

The patients were followed up to monitor local tumor control, survival, and neurological status at our hospitals or by the referring physicians. Neurological evaluations and MR imaging were performed 3, 6, and 12 months after stereotactic radiosurgery, then every 6 months for the next 2 years, and annually thereafter. Follow-up and survival periods were calculated from the day of stereotactic radiosurgery. Actuarial local control and survival rates were calculated by the Kaplan-Meier method from the day of stereotactic radiosurgery. Local control was defined as free from local tumor regrowth after stereotactic radiosurgery as evaluated by MR imaging. The differences between groups was assessed with the log-rank test. Differences were considered statistically significant if $p < 0.05$.

Table 1 Patients' and disease characteristics

Features	Value
Age at treatment (yrs)	
range	16–76
median	52
Male:female	21:77
Tumor location	
cavernous sinus	48
petroclival	29
cerebellopontine angle	11
orbit	6
others	12
Treatment settings	
post-biopsy	2
postoperative residual	25
postoperative recurrence	39
definitive GKS	35
post-GKS recurrence	3
post(operation + GKS) recurrence	2
Tumor volume (cm^3)	
range	0.3–45.0
median	3.9
Dose to the tumor margin (Gy)	
range	12–22.5
median	16
Pathological diagnosis	
meningothelial	58
fibrous	6
transitional	2
atypical	2
meningioma, NOS	1
no pathology	37

GKS: gamma knife surgery, NOS: not others specified.

Results

Local tumor progression was observed in 15 patients after a median follow-up period of 53.2 months (range 12.2–204.4 months) after stereotactic radiosurgery. Actuarial local tumor control rates were 86.9% and 78.9% at 5 years and 10 years, respectively (Fig. 1). The tumors with volume of 4 cm^3 or smaller had a higher local control rate than those with volume of larger than 4 cm^3 (97.5% vs. 76.1% at 5 years, $p = 0.001$) (Fig. 2A). Local control rates were also better in tumors with the entire volume included within the isodose line of 14 Gy or more than tumors with incomplete coverage by the 14 Gy isodose line (97.5% vs. 67.2% at 5 years, $p = 0.0006$) (Fig. 2B). Treatment dose at the tumor margin and stereotactic images used for treatment planning did not influence local tumor control (90.9% for doses higher than 16 Gy vs. 85.3% for doses of 16 Gy or lower at 5 years, $p = 0.41$; 88.0% by MR imaging vs. 85.3% by CT at 5 years, $p = 0.99$) (Fig. 3). Postoperative residual tumors treated with stereotactic radiosurgery as an adjuvant modality were controlled in all 25 cases, but the local control rate of the

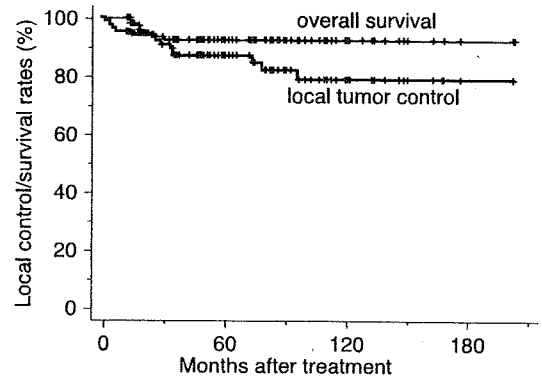

Fig. 1 Kaplan-Meier estimates of actuarial local tumor control and survival rates for all patients.

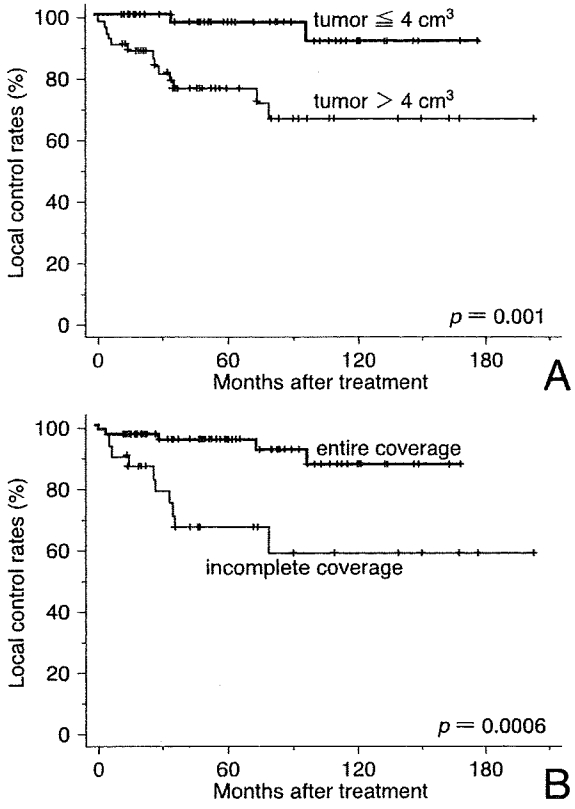

Fig. 2 Kaplan-Meier estimates of actuarial local tumor control rates by tumor volume (A) and tumor coverage at treatment (B) showing significant differences.

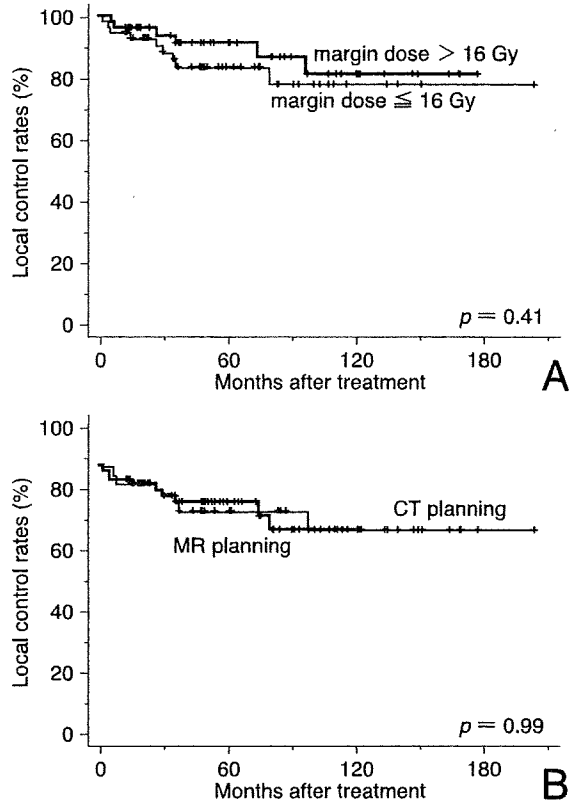

Fig. 3 Kaplan-Meier estimates of actuarial local tumor control rates by margin dose (A) and treatment planning method (B) showing no significant differences. CT: computed tomography, MR: magnetic resonance.

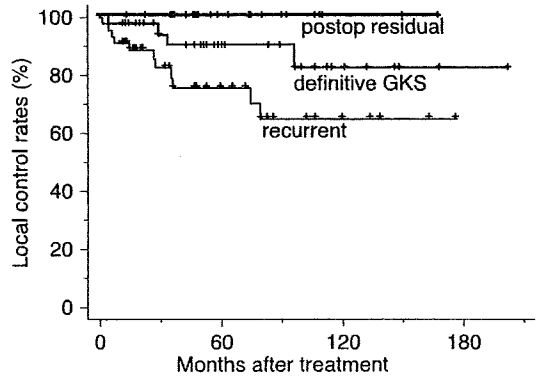

Fig. 4 Kaplan-Meier estimates of actuarial local tumor control rates by treatment setting. GKS: gamma knife surgery.

recurrent and untreated tumors treated with only stereotactic radiosurgery was 89.7% and 75.5% at 5 years, respectively, which was apparently inferior to the local control rate of 100% achieved by the two-staged strategy (Fig. 4). Overall survival rates were 92.5% and 92.5% at 5 years and 10 years, respectively (Fig. 1).

Eighty patients had cranial nerve deficits before stereotactic radiosurgery. Improvement was observed in 12 patients and worsening of the symptoms present at the treatment in 2 patients after the treatment. Cranial nerve deficits remained stable in the other 66 patients. Newly developed permanent radiation-induced cranial nerve deficits were noted in one patient after stereotactic radiosurgery. Cranial nerve functions are summarized in Table 2.

Discussion

The present study showed that tumor volume of 4 cm^3 or smaller and complete tumor coverage were associated with better local control (Fig. 2). In addition, local control was apparently superior in the patients treated by stereotactic radiosurgery for postoperative residual tumor compared to treatment for recurrent tumor or single modality stereotactic radiosurgery treatment (Fig. 4). This difference presumably reflected the tumor debulking by surgical intervention before stereotactic radiosurgery, resulting in the beneficial condition of smaller tumor volume at the time of stereotactic radiosur-

Table 2 Cranial nerve function after gamma knife surgery (GKS)

Cranial nerves	Symptomatic before GKS	Improved	Worsened**	Transient deficits***	Permanent deficits***
I	1	0	0	0	0
II	24	1	1	0	0
III	21	3	0	0	0
IV	19	2	0	0	0
V	42	7	1	3	0
VI	33	8	0	0	0
VII	10	1	0	0	1
VIII	25	2	0	0	0
IX	2	0	0	0	1
X	2	0	0	0	1
XI	0	0	0	0	0
XII	1	0	0	0	0
All	80	12*	2	3	1

*Improvement of at least one cranial nerve symptom with no worsening of any cranial nerve symptom. **Deterioration of symptom which had been observed before GKS. ***New development of symptom which had not existed before GKS.

gery.

Local control rates showed no significant difference between patients treated by MR imaging-based planning and by CT-based planning (Fig. 3B). Tumor volume delineated by MR imaging is known to differ considerably from that by CT.[29] In addition, MR imaging has a problem of image distortion, which can influence the setup error.[36] However, the stereotactic images used in the treatment planning did not affect the local tumor control in our experience, or in previous similar findings.[8]

The crude post-radiosurgical permanent complication rate of 3% (3/98 patients, Table 2) was not negligible, and longer follow-up periods might reveal higher complication rates, but our experience with skull base meningiomas was similar to that of other institutions. The median margin dose of 16 Gy was higher than that used at other institutions. We selected higher doses for skull base meningioma treatment because of the probable miserable consequences for local recurrence after stereotactic radiosurgery. Lower treatment dose is associated with reduced incidence of radiation-induced morbidities after stereotactic radiosurgery, and some investigators reported no influence on local tumor control.[11,22]

Local tumor control rates for skull base meningiomas after stereotactic radiosurgery were better in the patients with tumor volumes of 4 cm^3 or smaller, and the patients treated with adjuvant stereotactic radiosurgery for postoperative residual tumors. If the volume of the skull base meningioma is 4 cm^3 or smaller, the tumor can be treated by single modality stereotactic radiosurgery with good local control rate. If the tumor volume is larger than 4 cm^3, combined microsurgery and postoperative stereotactic radiosurgery is required if any residual tumor is detected postoperatively. Correct combination of the two modalities leads to excellent local tumor control.

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Commentary

This is a well presented and statistically sound article. Its merit lies in showing the usefulness of heightened radiation primarily or as supplemental treatment to microsurgery for skull base meningiomas. Base of Skull Surgery (BOSS) is an evolving discipline towards which this article does make a contribution. Although

suggested by the authors that skull base meningiomas even up to the size of 4 cm^2 can or should be treated by radiation treatment, it has to be clearly understood by neurosurgeons that surgery is superior and better for all tumors, from scalp to sole, including meningiomas. It is only in cases where surgery is not possible or is dangerous beyond reasonable limits, radiation may be used as a primary 'palliative' form of treatment.[1] Despite the success obtained by the authors, in recurrent or residual tumors, the role of radiation treatment for skull base meningiomas can at best be considered to be still under evaluation. It needs to be appreciated that the so-called base of the skull is fill-in-the-gap osseation between a jungle of neurovascular structures that traverse to-and-from the brain. All neurovascular structures are too precious to be trifled with by any radiation. Radiation offers short-term gain but spawns long-term, obstinate side-effects. One might summarize that anticytotic therapy (chemotherapy, radiotherapy) shall only be reserved for sites inaccessible to the knife.

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Igaki et al. have presented their results of stereotactic radiosurgery for skull base meningioma. Their overall results are good. Actual local tumor control rates were 86.5% and 78.9% at 5 years and 10 years, respectively, which are acceptable. The crude post-radiosurgical permanent complication rate was 3% (3/98 patients). More detailed analysis of cranial nerve complications is recommended, such as delineation of cranial nerves under the special MRI-based planning. Did any differences in these tumor control results depend on the pathological diagnosis (MIB-1 index)? Local control rates showed no significant difference between patients treated by MRI-based planning and by CT-based planning. How was the tumor margin covered, the so-called dural tail sign on MRI?

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In this report, Igaki and his coauthors report the outcomes for stereotactic radiosurgery (SRS) using the gamma knife technology for a series of 98 patients with 106 skull-base meningiomas treated during a six-year interval. The minimum follow-up was one year. The authors, working in a center of excellence, have defined outcomes which can be related to several potential radiosurgical features. First, they found that long-term tumor control was enhanced when smaller volume tumors were used. Providing that there was no confounding dose selection effect, it is clear that smaller tumors, perhaps treated earlier in their clinical course, may offer patients superior results.

The authors confirm that minimal tumor coverage of the entire imaging-defined volume with 14 Gy is effective in achieving tumor control rates of more than 90% of patients. Their usual prescription dose was somewhat higher than most centers currently use (16 Gy at the margin), a dose selected because of their concern that treatment failure would be higher in patients who received a lower margin dose. However, they could not confirm any better tumor control rates with lower doses than 16 Gy at the margin. The authors also note that there seems to be little difference between the tumor control rate based on CT planning versus patients who had MRI-based planning. Of interest, the patients who did best represent those who had initial tumor debulking, after which the gamma knife was used as adjuvant management for the residual tumor. The patients who did least well were those who were treated in a delayed fashion after evidence of tumor recurrence or progression was noted. We have found that early post microsurgical SRS for postoperative residuals also improves tumor control rates.

The goal of radiosurgery has been to improve long-term tumor control and survival, and to reduce cranial nerve and other neurologic morbidity associated with aggressive surgical removal. I believe that the doses used at the edge are probably higher than necessary to achieve the same long-term tumor control rates, based on our cumulative experience in more than 3000 skull base cases. If one uses a rule of thumb that 13 Gy at the edge of a tumor (its margin) is radiobiologically equivalent to giving 52 Gy fractionated radiation therapy, then one can expect tumor control rates in the range of 90% at five years. The great advantage, of course, of radiosurgery is precision, accuracy, a single-day procedure treatment, integration of the planning and radiosurgical dose delivery in a single session, and excellent long-term reports of outcomes from many world-wide sites. The adverse radiation effect risk was extremely low, perhaps 1% of patients.

Long-term follow-up continues, as it needs to, for patients undergoing total microsurgical removal as well. However, multicenter experience now over more than 25 years indicates that radiosurgery of skull-base tumors has an established role. This report provides additional evidence of the value of radiosurgery as a primary or adjuvant management for meningiomas.

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A Retrospective Comparison of Clinical Outcomes and Quality of Life Measures Between Definitive Chemoradiation Alone and Radical Surgery for Clinical Stage II–III Esophageal Carcinoma

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Background: This retrospective study was conducted to compare the treatment and quality of life (QOL) results between radical surgery and definitive chemoradiotherapy (CRT) for stage II–III carcinoma of the esophagus.
Methods: Between 2000 and 2009, 128 consecutive patients were selected for this study in which 72 were treated with definitive CRT and 56 with radical surgery. QOL was assessed using Functional Assessment of Cancer Therapy-Esophagus for 51 patients who were free of disease at the time of survey.
Results: With a median follow-up period of 37.8 months with 66 survivors, the 4y-DFS in the surgery group were 36% in the CRT group and 51% in the surgery group ($P = 0.0028$). In the CRT group, the number of cases of the advanced age, T4 stage, and stage III was significantly larger than the surgery group. QOL assessments were completed at rates of 100% in the CRT group and 88% in the surgery group. Overall E Total score had a significant difference between arms (CRT > surgery, $P = 0.045$).
Conclusions: CRT was inferior to surgery in survival but superior in QOL measures, although the CRT group had a larger number of patients with poorer prognostic factors.
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KEY WORDS: **quality of life; esophageal cancer; chemoradiation; esophagectomy**

INTRODUCTION

The optimal management of esophageal cancer is still controversial. Surgical resection has been widely accepted as the standard treatment for locally advanced esophageal cancer, as techniques have improved during the past decade. Nonetheless, the 5-year survival rate remains relatively modest at <40% [1]. In the past, the overall 3-year survival rate reported for esophageal cancer remained below 35%, despite treatment with aggressive resection alone [2,3]. The radical surgical treatment of esophageal carcinoma includes transthoracic esophagectomy with extensive lymphadenectomy [4], which is the standard surgical procedure in Japan. The perioperative mortality is around 5% at the well-known cancer centers.

Oncologists have recently advocated that a nonsurgical approach with definitive chemoradiotherapy (CRT) may be the standard for localized esophageal carcinoma [5–8]. Although surgery alone or CRT have generally been accepted as reasonable options for patients with locoregional esophageal cancer, the 5-year survival rate with either management is approximately 20–30% [9,10]. It is uncertain whether definitive CRT achieves treatment outcomes comparable to surgery, because there is only one small prospective randomized trial comparing CRT with esophagectomy [11]. The performance of a clinical randomized trial is quite difficult because of the differing treatment characteristics. Patients with resectable stage II–III esophageal cancer are made to select either definitive CRT or radical surgery as a primary therapy by themselves. When choosing treatment method, quality of life (QOL) after treatment is one of the important factors for these patients.

Few randomized studies have prospectively assessed and compared QOL between esophageal cancer treatment modalities [12–15]. This retrospective study was conducted to compare the treatment and QOL outcomes between radical surgery and definitive CRT for stage II–III esophageal cancer in a single institution during the same period.

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MATERIALS AND METHODS

Between June 2000 and December 2008, 128 consecutive patients were surveyed retrospectively for this study in which 72 were treated with CRT and 56 with surgery. Each esophageal carcinoma was staged according to the American Joint Committee on Cancer TNM clinical stage classification (1997). The last follow-up was performed on April 2009. Patients with clinical T1N1M0 or T2-4N0-1M0 were eligible. Patients deemed to have technically unresectable cancer, patients who refused to undergo surgery, or those considered medically unfit for surgery were eligible for definitive CRT. Patients with tracheoesophageal fistula or evidence of metastatic cancer were not eligible for this study.

CRT

External beam radiation was administered using four fields of 6–10 MV photons (two anterior–posterior opposed fields, and two anterior–posterior oblique opposed fields to remove the spinal cord from the radiation fields) to a total dose of 50.4 Gy using 1.8 Gy daily fractions in 5 weeks. Positioning of the fields and dosimetry were studied using a computed tomography (CT) scan and 3D treatment plan. The dose to the spinal cord was limited to 80 percent % of the total 50.4 Gy

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dose. The treatment fields encompassed the whole esophagus from the esophageal entry to the gastric–cardiac junction with 2-cm lateral margins. Supraclavicular nodes were included in the treatment portals for upper thoracic and cervical tumors; celiac nodes were included for lower carcinomas.

All 72 patients received chemotherapy (CT) concurrently with irradiation. The CT consisted of maximum four cycles of 5-fluorouracil (800 mg/m^2/day, days 1–4, continuous) combined with *cis*-diammine-glycolatoplatinum (nedaplatin) (80 mg/m^2, day 1, bolus); standard techniques were used for hydration and alkalization. The total cycle number of CT was only one (n = 5), two (n = 38), three (n = 9), or four (n = 20) cycles every 3–4 weeks. The 3rd and 4th cycles of CT were administered in the adjuvant setting after concurrent CRT.

In order to bring results of the CRT group close to the surgery group a little, the salvage surgery for residual tumor just after definitive CRT is positively examined in our department. In our study, two patients out of 72 patients (2.8%) in the CRT group were given salvage surgery for the residual tumor immediately after definitive concurent CRT (cCRT).

Surgery

Fifty-six patients underwent right or left thoracotomy for curative resection by total or subtotal thoracic esophagectomy, as well as regional lymphadenectomy. No patient underwent transhiatal esophagectomy. Regional lymph nodes included not only mediastinal but also perigastric nodes, and for this reason regional lymphadenectomy represented at least a two-field lymphadenectomy. Esophageal reconstruction was performed using the stomach, colon, or jejunum. Twenty-six surgical patients (46%) received postoperative adjuvant therapy. Our surgeons recommended postoperative adjuvant CT for 30 patients (54%) with pathologically confirmed metastasis to the lymph nodes and without postoperative severe complications. Twenty-six of these patients agreed on receiving adjuvant prophylactic CT, which consisted of 2 weeks of intravenous daily cisplatin (6 mg/m^2/day, days 1–5 and 8–12) and 5-fluorouracil (600 mg/m^2/day, days 1–5 and 8–12). The remaining 30 patients received no prophylactic adjuvant therapy.

QOL Assessment

QOL for all 51 patients who were free of disease at the time of survey (from October to April 2009) was assessed during their follow-up visit following treatment. They filled out the QOL questionnaires at their follow-up visit or mailed them back if there was a lack of time.

Functional Assessment of Cancer Therapy (FACT)–Esophagus Trial Outcome Index (E TOI) (score range: 0–124), FACT-General Total (G Total) (score range: 0–108), and FACT-Esophagus Total (E Total) (score range: 0–176) scores (mean ± 2 standard deviations) by treatment regimen.

Functional Assessment of Cancer Therapy-G (FACT-G)

The general version of the Functional Assessment of Cancer Therapy (FACT-G) Version 4 is a 27-item self-report questionnaire that consists of five subscales: physical well-being (PWB), social/family (SWB), emotional (EWB), and functional (FWB). Each item is rated on a Likerttype scale from 0 (not at all) to 4 (very much). The range of scores on the FACT-G is 0 to 108 (27 items × 4). The FACT-G was developed and validated to measure QOL in cancer patients and was designed for use in clinical trials [13]. Although it can be adapted for use in an interview format, it was utilized in this study as a self-report tool easily completed in 5–10 min. Patients were asked to rate how they feel today and over the previous 7 days.

The FACT-G subscale scores can be aggregated into a total QOL score, with a higher score indicating better QOL. Cronbach's alpha for each subscale has been reported as follows: PWB (0.82); FWB (0.80); SFWB (0.69); EWB (0.74); and total FACT-G (0.89).

Functional Assessment of Cancer Therapy-Esophagus (FACT-E)

FACT-E is the FACT-G plus an esophagus cancer-specific subscale (ECS) [16]. The esophagus subscale consists of 17 questions developed from interviews with patients and clinicians involved with esophageal cancer. The range of scores on the E subscale is 0–68 (17 items × 4).

A Trial Outcome Index (TOI) representing PWB + FWB + the E subscale was used as a measure of treatment impact on physical symptoms and functioning.

Statistical Analysis

Statistical analyses were performed using StatView Dataset File version 5.0J for Windows computers (Cary, NC). Disease-free survival (DFS) was calculated from the first date of curative treatment. Survival time was plotted using the Kaplan–Meier method. Differences in patients' characteristics were analyzed by the chi-square test or Fisher's exact test for 2 × 2 columns and unpaired *t*-test for a succession of numbers. Differences in survival by treatment were evaluated using the log-rank test. Statistical analysis of QOL score was performed with Fisher's exact test. Differences with values of $P < 0.05$ were considered statistically significant.

The univariate and multivariate analyses of DFS about the factors of age clinical-stage (c-stage), each TNM stage, and therapy method were performed on the entire group only (n = 128) by log-rank test and Cox proportional hazard model, respectively. The total cycle number of chemotherapy was analyzed on the CRT group only (n = 72).

RESULTS

With a median follow-up period of 37.8 months (range: 4.3–91.8 months) with 63 survivors (49%), the 4-year disease-free survival rates were 36% in the CRT group versus 51% in the surgery group with statistical significance ($P = 0.028$) (Fig. 1). The 4-year overall survival rates were also 29% in the CRT group versus 55% in the surgery group with statistical significance ($P = 0.046$).

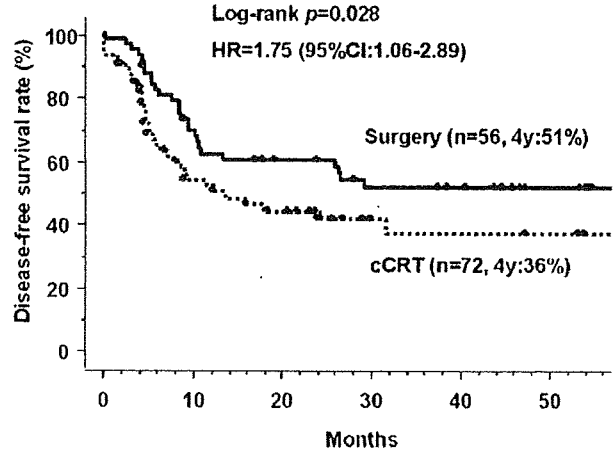

Fig. 1. Disease-free survival curves between the chemoradiotherapy and surgery group.

TABLE I. Patient Characteristics by Treatment Regimen

Characteristic	Chemoradiation, n (%)	Surgery, n (%)	P value
	72 (100)	56 (100)	
Gender			
Male	62 (86)	50 (89)	0.59
Female	10 (14)	6 (11)	
Age (years)			
Median	68	64	0.011 (unpaired *t*-test)
Mean	68.5	64.6	
Range	42–85	47–82	
Location			
Cervical	10 (14)	2 (4)	0.18
Upper thoracic	8 (11)	5 (9)	
Middle thoracic	23 (32)	23 (41)	
Lower thoracic	31 (43)	26 (46)	
c-Stage			
IIA	20 (28)	24 (43)	0.0047
IIB	11 (15)	15 (27)	
III	41 (57)	17 (30)	
c-T stage			
T1	5 (7)	7 (13)	0.0026
T2	18 (25)	10 (18)	
T3	35 (49)	38 (68)	
T4	14 (19)	1 (2)	
c-N stage			
N0	24 (33)	24 (43)	0.27
N1	48 (67)	32 (57)	
Histology			
Squamous cell carcinoma	65 (90)	54 (96)	0.10
Adenocarcinoma	5 (7)	0	
Others	2 (3)	3 (4)	

In the CRT group, the number of cases of the advanced age (mean; 68.5 years vs. 64.6 years, $P = 0.011$), T4 tumor (19% vs. 2%, $P = 0.0026$), and stage III (57% vs. 30%, $P = 0.0047$) was significantly larger than the surgery group in the DFS (Table I).

Ten patients in the definitive CRT group had cervical esophageal cancer. Only two patients who underwent surgery had cervical esophageal cancer. The majority of these people were allocated to non-surgical therapy because of the potential requirement of a more extended resection such as a laryngopharyngoesophageal resection.

In the CRT group, the total cycle number of CT was a prognostic factor (Fig. 2). When only one (n = 5) or two (n = 38) cycles of CT was administered, the disease-free survival was significantly inferior to three (n = 9) or four (n = 20) cycles ($P = 0.024$). In the surgery group, there was not a significant difference between with and without postoperative adjuvant CT in the DFS (45% vs. 57%, $P = 0.40$). The clinical stage III versus II ($P = 0.0002$) and clinical T3–4 versus T1–2 ($P = 0.0087$) as well ($P = 0.0028$) prognostic factors by univariate analysis (Table II). However, the significant differences disappeared by multivariate analysis (Table II).

In ten patients (18%), pathological TNM stage was different from clinical TNM stage before surgery. The detail of stage migration was from cT3N0 to pT3N1 in five patients and from cT2N1 to pT1N1 in two and from cT2N0 to pT1N1, from cT3N1 to pT4N1, and from cT2N1 to pT3N1 in one patient, respectively. Though excluded in this study, upstaging from cT1N0 (c-stage I) to pT1N1 (p-stage IIB) was seen in 10 patients during the same period.

Adverse Events Observed After Surgery

The mean ± SD and median interval between the date of surgery and discharge was 62.7 ± 53.5 (SE = 7.2) and 50 days (range; from 15 to 267 days) in the surgery group. Three patients were discharged due to death at 3.7, 4.4, and 5.2 months after surgery. Two patients suffered form treatment-related death at 4.4 and 9.2 months after surgery.

The grade 2 adverse events were seen in 7 patients (12.5%), grade 3 in 19 patients (33%), and grade 4 in 8 patients (14%) after surgery. The recurrent laryngeal nerve dysfunction (23%), anastomotic leak (23%), and pulmonary complication (21%) were seen with a high frequency.

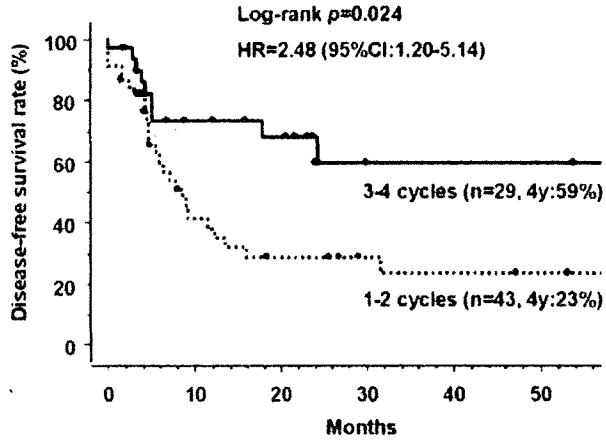

Fig. 2. Disease-free survival curves in the chemoradiotherapy group by the total cycle number of chemotherapy.

Adverse Events Observed After Definitive CRT

As to hematological adverse events, grade 3 and 4 leukopenia was seen in 42 patients (58%) and 10 patients (14%), anemia in 16 patients (22%) and 0 patient, and thorombocytopenia in 23 patients (32%) and 13 patients (18%) during CRT. On the other hand, as to non-hematological side effects, grade 3 and 4 side effects were seen in 10 patients (14%) and 5 patients (7%). Radiation esophagitis was seen with a high frequency. Only one patient suffered form treatment-related death by esophageal bleeding at 2.1 months after starting definitive CRT.

QOL Assessments

QOL assessments were completed at rates of 100% (22/22 cases) in the CRT group and 88% (29/33 cases) in the surgery group. E TOI score was 103 (mean) ± 20 (SD) in the CRT group versus 94 ± 20 in the surgery group ($P = 0.093$). G Total score was 83 ± 16 in the CRT group versus 78 ± 16 in the surgery group ($P = 0.23$). E Total score had a significant difference between arms. The score was 142 ± 24 in the CRT group versus 127 ± 25 in the surgery group ($P = 0.045$) (Fig. 3).

There was no significant difference in PWB, EWB, and FWB scores between the two groups, but there was a marginal difference in SWB ($P = 0.074$) and a significant difference in ECS ($P = 0.016$). Table III summarizes the QOL scores between the two groups.

The E TOI, G Total, and E Total scores of eight patients out of 11 with the recurrence were 81 ± 28, 71 ± 17, and 118 ± 30. Including these eight patients, there is no significant difference in the E TOI (96 ± 25 in the CRT group vs. 93 ± 19 in the surgery group, $P = 0.51$), G Total (80 ± 17 vs. 76 ± 16, $P = 0.37$), and E Total (135 ± 28 vs. 126 ± 24, $P = 0.16$) scores between the two groups by unpaired *t*-test.

There was no difference in QOL of E TOI (100 ± 17 with chemotherapy vs. 90 ± 17 without chemotherapy, $P = 0.15$), G Total (85 ± 17 vs. 75 ± 10, $P = 0.075$), and E Total (139 ± 24 vs. 123 ± 17, $P = 0.068$)

TABLE II. Univariate and Multivariate Analysis in Both Groups

Characteristic	n (%)	4-Year DFS	Univariate *P*-value	Multivariate *P*-value	HR (95% CI)
Age					
≥70	50 (39)	38%	0.45		
<70	78 (61)	46%			
Age					
≥75	24 (19)	29%	0.19		
<75	104 (81)	46%			
Stage					
II	70 (55)	60%	0.0002	0.076	0.55 (0.28–1.06)
III	58 (45)	23%			
T stage					
T1–2	40 (31)	65%	0.0087	0.28	0.65 (0.30–1.43)
T3–4	88 (69)	35%			
T stage					
T1–3	113 (88)	48%	0.0019		
T4	15 (12)	11%			
N stage					
N0	48 (38)	54%	0.12		
N1	80 (62)	37%			
Therapy method					
Surgery	56 (44)	51%	0.028	0.082	1.60 (0.94–2.70)
cCRT	72 (56)	36%			
Total cycle number of chemotherapy in the CRT group					
1–2	43 (60)	23%	0.024		
3–4	29 (40)	59%			

between the surgery alone versus the surgery plus adjuvant chemotherapy.

There was a significant difference in some individual scale items of GP5 = "I am bothered by side effects of treatment" (3.22 ± 1.09 in CRT vs. 3.88 ± 0.33 in surgery, $P = 0.0055$) and HN5 = "I am able to eat as much food as I want" (2.75 ± 1.65 in CRT vs. 1.64 ± 1.19 in surgery, $P = 0.0075$) between the CRT and the surgery groups. Additionally there was a marginally significant difference in some individual scale items of GP4 = "I have pain" (3.31 ± 0.93 in CRT vs. 3.70 ± 0.64 in surgery, $P = 0.096$), GS3 = "I get support from my friends" (2.04 ± 1.63 in CRT vs. 1.21 ± 1.32 in surgery, $P = 0.053$), HN10 = "I am able to communicate with others" (3.69 ± 0.60 in CRT vs. 3.24 ± 1.05 in surgery, $P = 0.055$), E7 = "I wake at night because of coughing" (3.52 ± 1.12 in CRT vs. 3.00 ± 0.91 in surgery, $P = 0.067$), and C2 = "I am losing weight" (3.48 ± 0.99 in CRT vs. 2.88 ± 1.45 in surgery, $P = 0.077$) between the two groups.

There was no association between clinically significant variables and QOL scores (E TOI, G Total, and E Total). Such clinically significant variables included histological type (squamous cell carcinoma vs. the others, $P = 0.54$ in E TOI, 0.80 in G Total, and 0.93 in E Total), c-stage (II vs. III, $P = 0.65$, 0.96, and 0.98), c-T stage (T1-2 vs. T3-4, $P = 0.29$, 0.28, and 0.26), c-N stage (N0 vs. N1, $P = 0.66$, 0.39, and 0.40), sex (male vs. female, $P = 0.25$, 0.59, and 0.33), age (≥75 years vs. < 75 years, $P = 1.00$, 0.56, and 0.55 and ≥70 years vs. <70 years, $P = 0.33$, 0.56, and 0.56), and location (Ce-Mt vs. Lt-Ae, $P = 0.51$, 0.73, and 0.76).

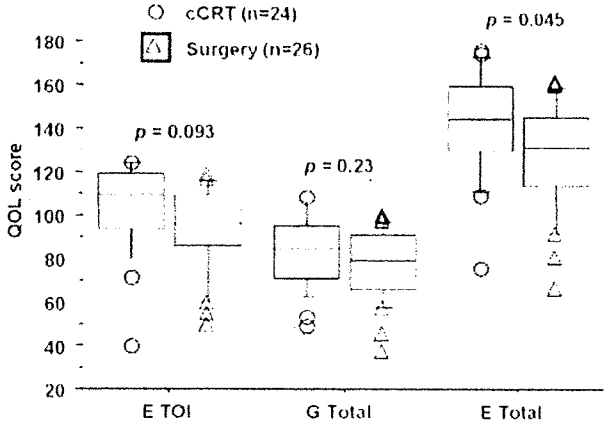

Fig. 3. Functional Assessment of Cancer Therapy (FACT)– Esophagus Trial Outcome Index (E TOI) (score range: 0–124), FACT-Genaral Total (G Total) (score range: 0–108), and FACT-Esophagus Total (E Total) (score range: 0–176) scores (mean ± standard deviations) by treatment regimen.

TABLE III. QOL Score by Treatment Regimen

	CRT	Surgery	*P* value
PWB (0–28)			
Mean	22.96	23.74	0.61
SD	6.35	4.75	
Median	24.5	25	
SWB (0–28)			
Mean	18.71	14.58	0.074
SD	8.43	8.07	
Median	22	17	
EWB (0–24)			
Mean	19.94	18.79	0.34
SD	3.89	4.73	
Median	20	19	
FWB (0–28)			
Mean	20.69	19.85	0.65
SD	6.66	6.66	
Median	21.5	21	
ECS (0–68)			
Mean	57.51	49.64	0.016
SD	12.41	10.50	
Median	62.5	49	

There was no association between postoperative complications and QOL scores. The E TOI, G Total, and E Total scores were 94.7 ± 18.6 versus 96.5 ± 16.9 ($P = 0.81$), 76.9 ± 15.4 versus 83.9 ± 10.6 ($P = 0.21$), and 127.9 ± 22.8 versus 133.9 ± 19.6 ($P = 0.50$) in the grade 0–2 (n = 14) versus grade 3–4 (n = 11) of postoperative complications, respectively. There was no association between grade 3–5 complications after both definitive CRT plus radical surgery groups and QOL scores ($P = 0.66$ in E TOI, $P = 0.65$ in G Total, and $P = 0.50$ in E Total), either.

DISCUSSION

This is a retrospective study aiming to compare treatment and QOL between radical surgery and definitive CRT for locally advanced carcinoma of the esophagus. This is a large series of 128 consecutive patients. This series is not well balanced as regards the clinical stage, patient physiology, histological makeup of the study group, the degree of chemotherapy received in our non-surgical population and the clinical T stage clearly indicating that the population is not identical. This series may suffer from a certain methodological weakness as regards the collection of the patient, the difference between the two groups as regards the clinical stage of the disease and in the switch observed in the treatment group as regards the salvage surgery for two patients in the CRT group and a significant number of patients receiving adjuvant therapy after surgery.

In our institution, the patients who underwent non-surgical therapy were either technically unresectable, refused surgery, or were medically unfit. This, however, involved 56% of our total populations that would seem to be a very high percentage in patients with Stage II and III disease. One of that reasons may be that a second opinion from the other institutions is received widely in our department. Also the surgeons in our institution saw all of these patients who underwent non-surgical therapy. More specifically, the therapeutic strategy for esophageal cancer was discussed at a multidisciplinary cancer board a time each 2 weeks.

The optimal management of esophageal cancer is still controversial. Locally advanced esophageal cancer is usually associated with a poor prognosis because of a high local recurrence rate, despite aggressive management with radical surgery with or without postoperative adjuvant therapy [1,2]. The current standard of care for patients who are not suitable candidates for surgery, or who do not wish to have surgery, is definitive CRT. However, the National Comprehensive Cancer Network (NCCN) practice guidelines in the United State indicate that both esophagectomy and CRT with dose of 50–50.4 Gy are considered to be the standard treatment [17]. The recommendations also include surgery after CRT and adjuvant CRT after primary surgery, particularly in patients with adenocarcinoma, as recommended approaches, although these modalities are still investigational. In countries such as North America, the use of neoadjuvant CRT followed by surgery has been frequent despite the lack of convincing data to demonstrate its efficacy [18–23]. Although a meta-analysis demonstrated a benefit for patients who received preoperative CRT compared with patients who did not [24], this matter is considered far from resolved. However, the morbidity of the CRT was significant. Severe pleural effusion, pericarditis, heart failure, and radiation pneumonitis were possible sequelae of the concurrent CRT. According to the report of 78 patients achieving a complete response from National Cancer Center Hospital East [25], the incidences of grade 3 or 4 of these toxicities were 10.3%, 10.3%, and 3.8%, respectively. Therefore, it is important for clinicians to determine how these two treatments impact on patients' QOL. However, few studies have compared QOL following definitive CRT and radical surgery.

The adjuvant chemotherapy was chosen to use in almost 50% of our surgical patients, most of which had squamous cell carcinoma. Adjuvant therapy for potentially resectable esophageal cancer in Japan has differed from that in Western countries. The mainstay of adjuvant therapy in Japan has been postoperative adjuvant chemotherapy before after-mentioned JCOG 9907 [26,27]. The efficacy of adjuvant chemotherapy remains controversial. There was no difference in the survival rates between surgery followed by chemotherapy and surgery alone, according to the randomized trial of the Japan Clinical Oncology Group (JCOG) 9204 [28]. However, a benefit was found for adjuvant chemotherapy in the disease-free survival rate mainly for patients with metastasis in the lymph nodes. Adjuvant chemotherapy using CDDP/5-FU appears to be effective in preventing recurrence.

In the present study, the 4-year disease-free survival rates were 36% in the CRT group versus 51% in the surgery group ($P = 0.028$). The direct comparison is difficult because this is a retrospective study. The patients in our study group were not comparable. In the CRT group, the number of cases of the advanced age (median; 68 years vs. 64 years, $P = 0.011$), T4 stage (19% vs. 2%, $P = 0.0026$), and stage III (57% vs. 30%, $P = 0.0047$) was significantly larger than the surgery group. Additionally, in the CRT group, both T4 tumor ($P = 0.027$) and stage III ($P = 0.0015$) were poor prognostic factors by univariate analysis. Staging classification was performed clinically in the CRT group, whereas pathologically in the surgery group. There was a bias on patient choice.

The surgery results of each institution in our country on stage II/III esophageal cancer were reported in the 61st Annual Meeting of the Japan Esophageal Society held in June 2007 (http://pcp.kyorin.ne.jp/jes61/). The 5-year overall survival rate was 64% in Juntendo University Hospital (n = 266), 55% in Tokyo Medical and Dental University Hospital Faculty of Medicine (n = 164), 44% in Osaka University Hospital (n = 245), 54% in Aichi Cancer Center Hospital (n = 117), 57% (only this rate was 3-year survival) in National Cancer Center Central Hospital (n = 381), and 53% in Tohoku University Hospital (n = 46). The 4-year DFS (55%) in our institution is not inferior to these results. According to the Japan Clinical Oncology Group (JCOG) 9907 [26,27] comparing preoperative neoadjuvant CT with postoperative adjuvant CT using cisplatin plus 5-fluorouracil for clinical stage II/III (except T4 tumor) squamous cell carcinoma of the thoracic esophagus (n = 330) carried out in Japan recently, the 3-year overall survival rate was 63% in the neoadjuvant CT group versus 48% in the postoperative CT group ($P = 0.0014$). When considering the results from Western countries, there are various obstacles in interpreting the findings in relation to practice in Japan, as there are great differences in modes of surgical resections and survival results between Western countries and Japan as well as differences in tumor biology, in rates of squamous cell carcinoma and adenocarcinoma. In Japan, radical surgery with extensive nodal dissection is commonly indicated and most tumors are squamous cell carcinoma.

The mean and median length of stay was 8.9 and 7.1 weeks after surgery in our institution. In general, patients would be discharged within 3–4 weeks without postoperative severe complication after subtotal esophagectomy plus 2–3 regional lymphadenectomy in our institution. In fact, 9 (16%) and 17 (30%) patients were discharged within 3 and 4 weeks.

A prospective single arm phase II trial of definitive CRT for stage II/III (except T4 tumor) esophageal cancer (JCOG 9906) [29] carried out in Japan recently showed that the 3-year overall survival rate was 45%. In the present study including 14 cases (19%) with T4 tumor, the 4-year DFS was 12% in the CRT group. For patients with T4 disease, although aggressive surgical resection has been attempted in Japan, the outcome was very poor, with 5-year survival rates of less than 10% and high mortality and morbidity rates [30]. Ando et al. [31] reported outcomes of surgery in a sample of 419 patients from a single Japanese institution, Keio University School of Medicine. In their series, although more than half of the patients underwent radical dissection, no patients with T4 disease survived for longer than 5 years. Nishimura et al. [32] reported a prospective trial of definitive CRT, consisting of 5-FU, cisplatin, and concurrent external-beam radiation, at a total of 60 Gy, for 28 patients with T4 esophageal cancer with or without fistulae at Kinki University

School of Medicine. This study provided a complete response rate of 32%, and 2-year survival of 27% in patients with stage III disease (T4NanyM0).

As demonstrated by recent German and French phase III studies [33,34], surgery should not be considered as standard treatment among responder patients to CRT but seemed to improve survival suggesting that non-responder could have a potential benefit of curative surgery. The German study [33] compared non-surgery (CT-CRT) versus CT-CRT plus surgery. The randomization was performed initially. In the French study [34], the randomization was performed only in patients who had a tumor responses to moderate dose upfront CRT. According to the second study FFCD 9102 [34], there were no significant differences in QOL between the two arms (initial CRT followed by surgery and additional CRT arms), although the scores were superior in the CRT group during the first 2 years of treatment. In order to bring results of the CRT group close to the surgery group a little, the salvage surgery for residual tumor just after definitive CRT is positively examined in our department. The enforcement rate of salvage surgery after definitive CRT was 15% in the JCOG 9906 [29] and 17% (6/36 cases) in the CURE study [11]. In our study, two patients out of 72 patients (2.8%) in the CRT group was given salvage surgery.

In the CRT group, both E TOI score and G Total score were slightly superior to the surgery group in this study. Additionally, E Total score was significantly superior to the surgery group. Looking in detail, SWB (social/family well-being) score had a marginal difference and ECS (esophagus cancer subscale) score had a significant difference between the two regimens. In the both scores, the CRT group was superior to the surgery group. This suggests that organ preservation may lead to a better QOL. Among factors that may impact on QOL following treatment for esophageal cancer, esophageal stenosis may play a prominent role. Besides, the collecting rate of a questionnaire in the CRT group was 100% (22/22 cases) and, on the other hand, only 88% (29/33 cases) in the surgery group. Though QOL should be reported with longitudinal assessment including a baseline evaluation, this is a retrospective study and so that could not have been done. Since it was measured at different time points after treatment and only in patients free of disease, it is again biased. The QOL comparison was made only on the patients who survived disease-free for a mean of over 3 years. It may select only the patients who did well and does not examine the entire population.

The limitations of our study included the retrospective nature of the study, heterogeneity of the patient population in the two treatment arms and physician's bias in the selection of the patients. A matched-pair analysis would be better to compare the two groups but could not be done in our study because of the small number of patients. Nevertheless, we hope that our experience will initiate further prospective studies. This non-randomized study on patients with stage II–III carcinoma of the esophagus showed that CRT was inferior to surgery in survival but superior in QOL measures, although the CRT group had a larger number of patients with poorer prognostic factors.

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