Strahlentherapie
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**Original Article**

# Variability in Bladder Volumes of Full Bladders in Definitive Radiotherapy for Cases of Localized Prostate Cancer

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**Background and Purpose:** To evaluate variation in bladder volume of full bladders in definitive radiotherapy for localized prostate cancer and to investigate potential predictors of increased bladder volume variations.
**Patients and Methods:** In 40 patients, the bladder volume was measured with megavoltage computed tomography (MVCT) imaging performed just before irradiation during the administration of the 1st fraction (#1), the 10th fraction (#10), the 20th fraction (#20), and the 30th fraction (#30). Patients were instructed to avoid urinating for 60–90 minutes before the planning CT (pln-CT) scan and before daily irradiation. Patients were also encouraged to drink an unspecified volume of liquid that would result in a clear but tolerable urge to urinate.
**Results:** The population-mean bladder volume (±1SD) was 219 ml (±83 ml) at the planning CT scan (pln-CT), 186 ml (±96 ml) at #1, 149 ml (±73 ml) at #10, 137 ml (±59 ml) at #20, and 136 ml (±60 ml) at #30. The mean intrapatient variation in bladder volume (1 SD relative to the mean bladder volume of each patient) was 38% (range: 10–84%). The bladder volume at the pln-CT was correlated with the intrapatient variance in bladder volume with a correlation coefficient of 0.54 and $p<0.001$.
**Conclusion:** We observed a significant decline in bladder volumes during the course of radiotherapy. The bladder volume at the pln-CT was a significant predictor of increased bladder volume variations.

**Key Words:** Radiotherapy · Prostate cancer · IMRT · Bladder volume · Full bladder · MVCT

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**Schwankungen des Volumens gefüllter Blasen in der definitiven Radiotherapie bei lokalisiertem Prostatakarzinom**

**Hintergrund und Zweck:** Die Evaluierung der Schwankungen des Blasenvolumens gefüllter Blasen in der definitiven Radiotherapie bei lokalisiertem Prostatakrebs sowie die Untersuchung potenzieller Prädiktoren für erhöhte Schwankungen des Blasenvolumens.
**Patienten und Methoden:** Das Blasenvolumen von vierzig Patienten wurde mittels Megavoltage-Computertomographie (MVCT) bestimmt, die bei der Verabreichung der 1. Fraktion (#1), der 10. Fraktion (#10), der 20. Fraktion (#20) und der 30. Fraktion (#30) kurz vor der Bestrahlung durchgeführt wurde. Die Patienten wurden angewiesen, 60–90 Minuten vor dem Planungs-CT (pln-CT)-Scan und vor der täglichen Bestrahlung nicht zu urinieren. Die Patienten wurden zudem ermuntert, eine nicht näher bestimmte Menge an Flüssigkeit zu sich zu nehmen, um einen deutlichen aber tolerierbaren Harndrang herbeizuführen.
**Ergebnisse:** Der Mittelwert der Grundgesamtheit des Blasenvolumens (±1SA) lag beim Planungs-CT-Scan (pln-CT) bei 219 ml (±83 ml), 186 ml (±96 ml) bei #1, 149 ml (±73 ml) bei #10, 137 ml (±59 ml) bei #20 und 136 ml (±60 ml) bei #30. Der Mittelwert der Schwankung des Blasenvolumens innerhalb eines Patienten (1SA bezogen auf den Mittelwert des Blasenvolumens des einzelnen Patienten) lag bei 38 % (Spannweite: 10–84 %). Das Blasenvolumen zum Zeitpunkt des pln-CT wurde mit der Streuung des Blasenvolumens innerhalb eines Patienten korreliert, woraus sich ein Korrelationskoeffizient von 0,54 mit $p<0,001$ ergab.
**Fazit:** Im Laufe der Radiotherapie konnte eine deutliche Verringerung der Blasenvolumen festgestellt werden. Das Blasenvolumen zum Zeitpunkt des pln-CT-Scans erwies sich als signifikanter Prädiktor erhöhter Schwankungen im Blasenvolumen.

**Schlüsselwörter:** Radiotherapie · Prostatakarzinom · IMRT · Blasenvolumen · Gefüllte Harnblase · MVCT

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## Introduction

The bladder is filled to various volumes during fractionated radiotherapy. Changes in the bladder volumes affect both bladder dose volume and the position of adjacent organs (the prostate, seminal vesicles, small intestine, sigmoid colon, and rectum). Furthermore, significant variations in bladder volume can confound the planned dose distributions for three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) [8, 9, 14, 20, 23]. Therefore, bladder volume must be kept consistent throughout planning and treatment to reduce positional uncertainties related to the prostate and the risk of increased toxicity in the normal surrounding tissue.

There is no current consensus regarding optimal bladder volumes. One possible advantage of maintaining a full bladder is that part of the bladder is moved away from the target volume, thus, reducing bladder toxicity [6, 11, 12]. Moreover, a full bladder moves the small intestine and the sigmoid colon out of the irradiation field, also reducing toxicity in these organs [3, 5, 10, 13]. For these reasons, we ask patients scheduled to undergo irradiation for prostate cancer to maintain a full bladder during irradiation. However, in patients with full bladders, large variations in bladder volume vs. time trends have been observed during the course of radiotherapy course [11, 16, 18].

The aim of this study was to quantify the variations and trends in full bladder volume during the course of radiotherapy in patients being treated for prostate cancer. The second aim was to investigate the potential predictors of increased bladder volume variations.

## Methods and Materials

### Patient Characteristics

Between December 2007 and March 2008, 40 patients with localized prostate cancer (cT1-3N0M0) were enrolled into this study (Table 1).

**Table 1.** Patient characteristics. cT: stage clinical tumor stage; PSA: prostate-specific antigen; IPSS: International Prostate Symptom Score.

**Tabelle 1.** Patientenmerkmale. cT-Stadium: klinisches Tumorstadium; PSA: prostataspezifisches Antigen; IPSS: International Prostate Symptom Score (Internationaler Prostata-Symptomscore).

| | No. (%) |
|---|---|
| cT stage (TNM 6th ed.) | |
| 1–2a | 19 (48) |
| 2b | 4 (10) |
| 2c–3 | 17 (43) |
| Gleason score | |
| 2–6 | 15 (38) |
| 7 | 9 (23) |
| 8–10 | 16 (40) |
| Initial PSA | |
| 0–10 | 25 (63) |
| 10–20 | 10 (25) |
| >20 | 5 (13) |
| D'Amico's risk group | |
| Low | 10 (25) |
| Intermediate | 8 (20) |
| High | 22 (55) |
| IPSS | |
| 0–8 | 22 (55) |
| 9-1-9 | 13 (33) |
| 20–30 | 5 (13) |
| Neoadjuvant hormone therapy | |
| Yes | 21 (53) |
| No | 19 (48) |
| Age mean (range) | 71 (53–83) |

### Radiotherapy

All patients received definitive radiotherapy with helical tomotherapy using the Hi-Art System (TomoTherapy, Inc., Madison, WI, USA) at Edogawa Hospital (Tokyo, Japan). Patients were classified according to D'Amico's risk-group definition [4]. The clinical target volume (CTV) was defined as prostate only for low-risk patients, and prostate with a 5 mm margin and a 2 cm wide section of the proximal seminal vesicle for the intermediate-risk and high-risk patients. The planning target volume (PTV) was defined as the CTV plus a 5 mm margin. The prescribed dose, which was defined as 95% of the PTV receiving 100% of the prescribed dose (D95), was 72 Gy in 36 fractions for the low-risk patients and 76 Gy in 38 fractions for the intermediate-risk and high-risk patients. Treatment planning optimization was performed to satisfy the dose constraints defined by the in-house protocols for both the PTV and the organs at risk (OAR). The dose constraints for the PTV are a mean dose <79.8 Gy (105% of the prescribed dose) and a maximum dose <83.6 Gy (110% of the prescribed dose). The dose constrains for OAR are (1) the rectum wall defined as 0.5 cm above and below the PTV of no more than 10% of the volume to receive a dose >78 Gy, no more than 25% of the volume to receive a dose >70 Gy, no more than 35% of the volume to receive a dose >60 Gy, and no more than 65% of the volume to receive a dose >40 Gy; (2) the bladder wall of no more than 35% of the volume to receive a dose >70 Gy, and no more than 65% of the volume to receive a dose >40 Gy; (3) the sigmoid colon of no more than 0.5 ml to receive a dose >65 Gy; and (4) the small bowel of no more than 0.5 ml to receive a dose >60 Gy. A total of 21 patients (53%) underwent hormone therapy sequentially and/or concurrently. The patients were irradiated in a supine position with a knee support. A megavoltage computed tomography (MVCT) scan was performed just before the daily irradiation. In addition, soft tissue-based 3D–3D matching of the MVCT images with the planning CT (pln-CT) images was performed with the couch shifted to the optimal position.

### Patient preparations

The patients were instructed to refrain from urinating for 60–90 minutes before the planning CT scan (pln-CT) and before daily irradiation. The patients were also encouraged to drink an unspecified volume of liquids to ensure a clear but tolerable urge to urinate. The patients were instructed to take laxatives before the pln-CT, although no specific instructions regarding bowel movements before daily irradiation were issued.

### Bladder volume measurement

Bladder volume at the pln-CT was measured by kilovoltage CT (kVCT) imaging with a thickness of 2.5 mm. Bladder volume was also measured by MVCT imaging with a thickness of 4 mm four times during the course of radiotherapy: at the 1st fraction (#1), at the 10th fraction (#10), at the 20th fraction (#20), and at the 30th fraction (#30). All bladder volumes were measured by the same radiation oncologist (N.N.) by delineating whole bladder outlines in Focal (CMS Inc., St. Louis, MO, USA) (Figure 1).

We assessed the variability in population bladder volumes throughout pln-CT and radiotherapy by calculating mean population bladder volumes and standard deviations (SD). The mean of five measurements for each patient is shown as $V_{mean}$. As a measure of variation in intrapatient bladder volumes, the SD of $V_{mean}$ (denoted as $\sigma_{bl}$) is used, whereas, $\sigma_{bl\text{-}rel}$ was defined as$\sigma_{bl}$ relative to $V_{mean}$.

### Potential predictors

We also assessed the correlations between intrapatient bladder volume variations ($\sigma_{bl\text{-}rel}$) and potential univariate predictors. The following potential predictors were evaluated: age (continuous), T stage (T1–T2a, T2b, T2c–T3), Gleason score (2–6, 7, 8–10), pretreatment prostate-specific antigen (PSA) (continuous), risk group (low, intermediate, high), international prostate symptom score (IPSS) [2] (continuous), hormone therapy (with or without), bladder volume at the pln-CT (continuous), prostate volume (continuous), PTV volume (continuous), and acute cystitis (grade 0–1, grade 2, grade 3–5)

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### Statistical analysis

We used Prism version 5 (GraphPad Software Inc., La Jolla, CA, USA) for statistical analysis. Differences were considered significant if the relevant two-tailed p values were less than 0.05. The incidence of acute cystitis was described according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

## Results

All patients completed radiotherapy free of unscheduled interruptions exceeding 2 days. We successfully acquired all planned bladder volume measurements. The mean prostate volume was 27 ml (range: 9–77 ml), the mean PTV volume was 108 ml (range: 49–240 ml). The incidence of acute cystitis during radiotherapy was grade 2 in 7 patients (18%). No cases of grade 3–5 acute cystitis were observed.

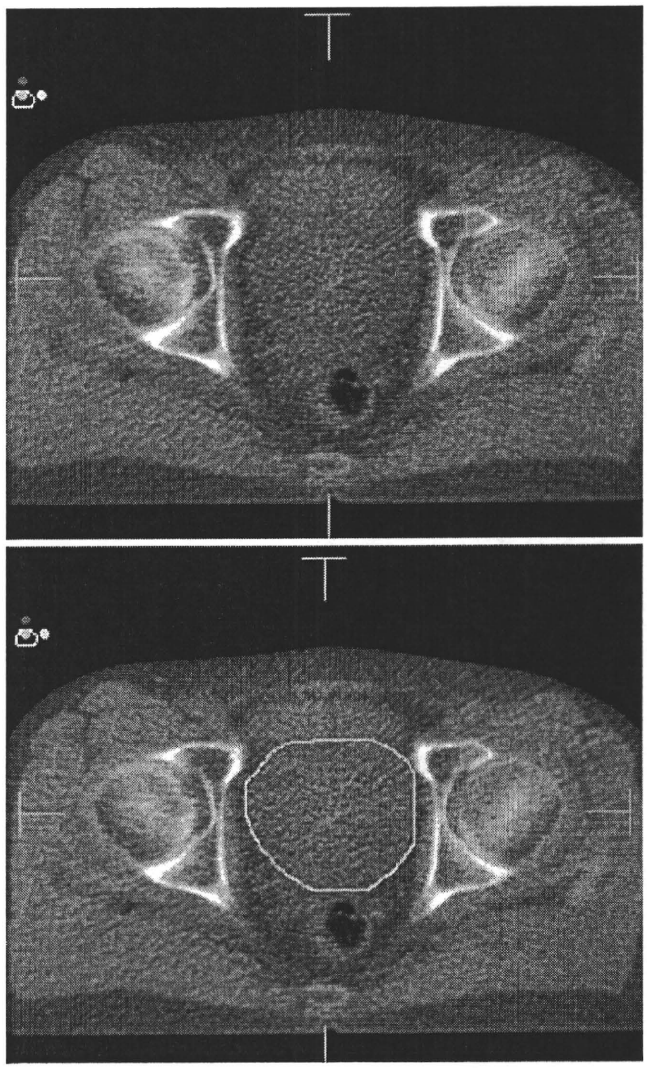

**Figure 1.** An example of mega voltage computed tomography (MVCT) imaging.

**Abbildung 1.** Beispiel einer Megavoltage-Computertomographie (MVCT).

### Bladder volume trends

The mean population bladder volume (±1 SD) was 219 ml (±83 ml) at the pln-CT, 186 ml (±96 ml) at #1, 149 ml (±73 ml) at #10, 137 ml (±59 ml) at #20, and 136 ml (±60 ml) at #30 (Figure 2). A mean population bladder volume reduction of 38% was observed from the pln-CT to #30 ($p<0.001$ by Wilcoxon's matched pairs test). A significant mean population bladder volume reduction was also found from #1 to #30 ($p<0.001$ by Wilcoxon's matched pairs test). The mean$\sigma_{bl}$ was 62 ml (range: 11–141ml), while the mean$\sigma_{bl\text{-}rel}$ was 38%

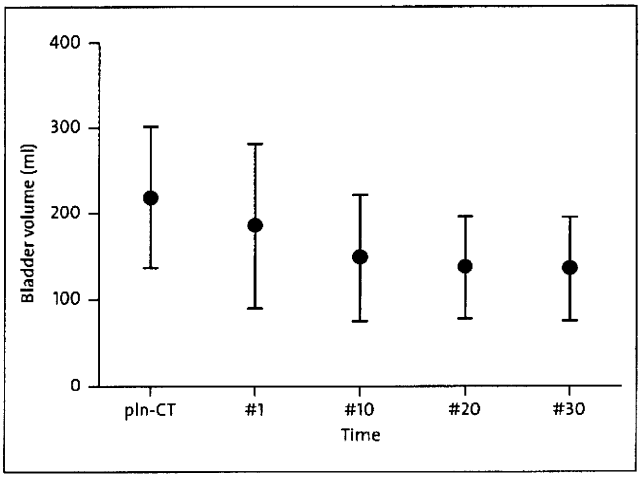


**Figure 2.** Population-mean bladder volume measured at the planning computed tomography scan (pln-CT) and during the course of radiotherapy. Error bars indicate one standard deviation. *#1, #10, #20, #30* = at the 1st fraction, at the 10th fraction, at the 20th fraction, and at the 30th fraction of radiotherapy, respectively.

**Abbildung 2.** Mittelwert der Grundgesamtheit des Blasenvolumens, der zum Zeitpunkt des Planungs-Computertomographie-Scans (pln-CT) und während des Verlaufs der Radiotherapie gemessen wurde. Die Fehlerbalken weisen auf eine Standardabweichung hin. *#1, #10, #20, #30* = bei der Verabreichung der 1. Fraktion, der 10. Fraktion, der 20. Fraktion bzw. der 30. Fraktion der Radiotherapie.

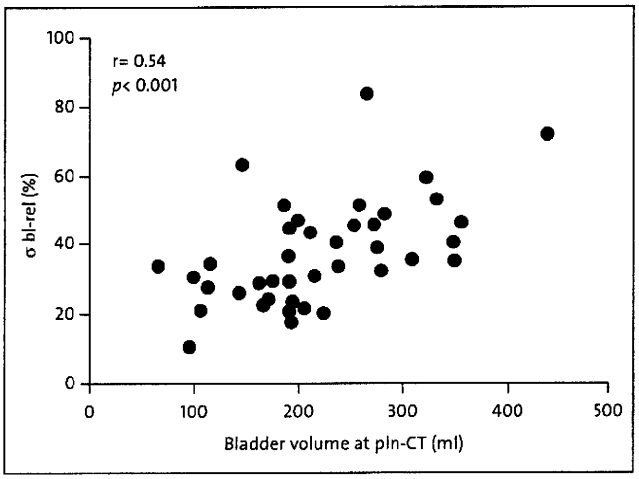


**Figure 3.** Correlation graph showing bladder volumes at the planning computed tomography scan (pln-CT) vs. intrapatient bladder volume variations ($\sigma_{bl\text{-}rel}$). $\sigma_{bl\text{-}rel}$ $\sigma_{bl}$ relative to $V_{mean}$, $\sigma_{bl}$ standard deviation of $V_{mean}$, $V_{mean}$ the mean of five measurements of a patient.

**Abbildung 3.** Auf diesem Korrelationsdiagramm ist die Beziehung zwischen den Blasenvolumen zum Zeitpunkt des Planungs-Computertomographie-Scans (pln-CT) und den Schwankungen des Blasenvolumens innerhalb eines Patienten abgebildet ($\sigma_{bl\text{-}rel}$). $\sigma_{bl\text{-}rel}$ $\sigma_{bl}$ relativ zu $V_{mean}$, $\sigma_{bl}$ Standardabweichung von $V_{mean}$, $V_{mean}$ der Mittelwert von fünf an einem Patienten vorgenommenen Messungen.

(range: 10–84%). We observed a statistically significant correlation between intrapatient variation in bladder volume ($\sigma_{bl\text{-}rel}$) and bladder volume at the pln-CT (Pearson r=0.54, $p<0.001$) (Figure 3). The intrapatient variation in bladder volume ($\sigma_{bl\text{-}rel}$) was not significantly associated with age ($p=0.68$), T stage ($p=0.88$), Gleason score ($p=0.78$), pretreatment PSA ($p=0.12$), risk group ($p=0.67$), IPSS ($p=0.66$), hormone therapy ($p=0.34$), prostate volume ($p=0.80$), PTV volume ($p=0.74$), or acute cystitis ($p=0.11$).

## Discussion

In order to improve bladder volume consistency when the goal is to maintain a full bladder, many institutions specify the volume of liquids to be consumed and the times at which such liquids should be consumed (e.g., drink 500 ml of fluid an hour before the planning CT scan and treatment) [1, 5, 15, 19, 22]. However, large variations in bladder volume have been reported with such protocols [1]. O'Doherty et al. [16] report that a fixed drinking protocol did not eliminate all variations in the bladder volume, in part due to significant individual variations in velocity of bladder filling. They [16] also reported that patients are able to accurately judge their bladder filling state and suggested that subjective patient assessments should be taken into account during efforts to control bladder volume. Stam et al. [18] found a weak but significant correlation between subjective scores for urge to urinate and bladder volume. For these reasons, our institution applied a protocol that did not specify liquid volumes. Instead, the patients were told to adjust the amount of liquid ingested based on their urge to urinate. Nonetheless, our study showed large variations in bladder volume. In an alternative approach, Stam et al. [18] measured daily bladder volumes during daily treatment using a bladder ultrasound scanner and provided patients with feedback to achieve reproducible bladder volumes. The feedback consisted of informing the patients of their daily bladder volume coupled with drinking advice. However, the daily variations in bladder volume did not differ significantly between the control group and the feedback group ($p=0.20$). Table 2 summarizes the findings of previous reports on variations in intrapatient bladder volume, suggesting that no protocol can ensure consistent bladder volumes when the goal is to maintain a full bladder.

Our study showed a decline in bladder volumes during the treatment course. Several previous reports [11, 16, 18] on bladder volume variance in definitive radiotherapy for prostate cancer have found the same trend. This trend was also reported in postoperative radiotherapy for prostate cancer [7] and in radiotherapy for uterine cervical cancer [1]. Although various protocols intended to achieve reproducible bladder volumes were used in these studies, a decreasing trend in bladder volume was a common finding. The reason for the decline in bladder volume remains unclear and may be multifactorial. Although Pinkawa et al. [17] hypothesized that cystitis might lead to a decline in bladder volume, our study showed no sig-

**Table 2.** Previous reports on bladder volume variation.

*intrapatient one standard deviation (one standard deviation relative to mean bladder volume).

**Tabelle 2.** Frühere Berichte zur Variation des Blasenvolumens.

*eine Standardabweichung innerhalb eines Patienten (eine Standardabweichung gegenüber dem Mittelwert des Blasenvolumens).

| Author | Diagnosis | Volume drunk | No. of patients | No. of measurements | Initial bladder volume | Bladder volume reduction | Bladder volume variation* |
|---|---|---|---|---|---|---|---|
| Lebesque et al. [9] | Prostate cancer | not fixed | 11 | 3 | 255 ml | 28% | 89 ml (33%) |
| Stam et al. [14] | Prostate cancer | not fixed (control group) | 18 | Daily | 348 ml | 31% | 149 ml (47%) |
| | | gave patients drinking advice according to their daily bladder volume (feedback group) | 16 | Daily | 367 ml | 19% | 156 ml (40%) |
| Ahmad et al. [19] | Uterine cervical | 500 ml (1 hour before) | 24 | Twice weekly | 378 ml | 71% | 168 ml |
| This study | Prostate cancer | not fixed | 40 | 4 | 219 ml | 38% | 62 ml (38%) |

* intrapatient one standard deviation (one standard deviation relative to mean bladder volume).

nificant correlation between intrapatient variations in bladder volume and the incidence of acute cystitis, and the mechanism underlying the decline in bladder volume can not be explained by cystitis alone, since our study and previous reports [1, 11, 16, 18] showed that reductions in bladder volume occurred immediately after treatment had been initiated. Bladder volume reductions during a treatment course may result in inadequate bladder dose–volume histograms (DVH) and may move the small intestine and sigmoid colon into the high dose irradiated field, increasing the potential toxicity for these organs. Based on the clear trend toward a decline in bladder volume during the course of radiotherapy, a more effective approach may be to perform planning CT scans in the middle of the fractionated radiotherapy course and perform replanning when large bladder volume variations are found.

In our study, larger bladder volumes at planning CT scans correlated with larger bladder volume variations, and previous studies reported similar findings [11, 16, 18, 21]. On the other hand, excessively small bladder volumes make it difficult to satisfy the planning dose constraints for adjacent organs (the bladder, small intestine, and sigmoid colon). For these reasons, several institutions target a half-full bladder or a comfortably full bladder [16, 18]. A half-full bladder appears to represent a reasonable target, offering the potential to improve bladder volume consistency in order to satisfy the dose constraints of the adjacent organs.

We used two different modalities to measure bladder volume: kVCT and MVCT. While the difference between these two modalities may have affected our results, the finding of bladder volume reductions during the treatment course was clear and definite. We also found significant population-mean bladder volume reductions from #1 to #30, which were both measured by MVCT imaging.

## Conclusions

A significant decline in bladder volumes during the course of radiotherapy was observed. The bladder volume at the pln-CT was a significant predictor of increased bladder volume variations. It may be possible to harness this trend to reduce bladder volume variance in order to avoid over-full bladders.

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**CLINICAL INVESTIGATION**

# OUTCOMES OF DIFFUSION TENSOR TRACTOGRAPHY–INTEGRATED STEREOTACTIC RADIOSURGERY

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**Purpose: To analyze the effect of use of tractography of the critical brain white matter fibers created from diffusion tensor magnetic resonance imaging on reduction of morbidity associated with radiosurgery.**
**Methods and Materials: Tractography of the pyramidal tract has been integrated since February 2004 if lesions are adjacent to it, the optic radiation since May 2006, and the arcuate fasciculus since October 2007. By visually confirming the precise location of these fibers, the dose to these fiber tracts was optimized. One hundred forty-four consecutive patients with cerebral arteriovenous malformations who underwent radiosurgery with this technique between February 2004 and December 2009 were analyzed.**
**Results: Tractography was prospectively integrated in 71 of 155 treatments for 144 patients. The pyramidal tract was visualized in 45, the optic radiation in 22, and the arcuate fasciculus in 13 (two tracts in 9). During the follow-up period of 3 to 72 months (median, 23 months) after the procedure, 1 patient showed permanent worsening of preexisting dysesthesia, and another patient exhibited mild transient hemiparesis 12 months later but fully recovered after oral administration of corticosteroid agents. Two patients had transient speech disturbance before starting integration of the arcuate fasciculus tractography, but no patient thereafter.**
**Conclusion: Integrating tractography helped prevent morbidity of radiosurgery in patients with brain arteriovenous malformations.** © 2011 Elsevier Inc.

**Arteriovenous malformation, Diffusion tensor tractography, Gamma knife, Morbidity, Stereotactic radiosurgery.**

## INTRODUCTION

Stereotactic radiosurgery is one of the principal treatment modalities for various kinds of vascular, neoplastic, or functional disorders of the brain (1–4). Although its efficacy is well known, radiation-induced neuropathy occurs in 5–20% of patients (2, 5–8). To minimize such unignorable risk, we have integrated tractography of the brain white matter based on diffusion tensor magnetic resonance imaging before the procedure into treatment planning of radiosurgery using Gamma Knife (9–11). Diffusion tensor tractography, one of the major recent advancements in magnetic resonance imaging, enables clear visualization of various fibers inside the white matter of the brain, which is not visible with use of conventional imaging modalities (12). Clinical applications of diffusion tensor tractography are mainly reported as diagnostic tools, and reports on its therapeutic application are quite limited (10, 13). In this study, we analyzed the effect of integrating diffusion tensor tractography into treatment planning of stereotactic radiosurgery on the reduction of morbidity in a prospective case series with arteriovenous malformations of the brain.

## METHODS AND MATERIALS

Our selection criterion for stereotactic radiosurgery was, in principle, small malformations (<3 cm) in critical, or eloquent, areas of the brain (including sensorimotor, language, or visual cortex; the hypothalamus or thalamus; the internal capsule; the brain stem; the cerebellar peduncles; and the deep cerebellar nuclei) that, if injured, result in disabling neurologic deficits (2, 14). We started integrating diffusion tensor tractography of the pyramidal tract in February 2004 because we considered the pyramidal tract to be the most crucial fiber in preventing morbidity of radiosurgery out of complexity of white matter fibers inside the brain. From May 2006, we added the integration of diffusion tensor tractography of the optic radiation, and diffusion tensor tractography of the arcuate fasciculus tractography from October 2007. One hundred forty-four patients with arteriovenous malformations who have consecutively undergone stereotactic radiosurgery using Gamma Knife with this protocol between February 2004 and December

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Table 1. Baseline characteristics of 144 patients treated

| | |
|---|---|
| Age (y) | 35 (5–77) |
| Female sex | 65 (45) |
| Details of arteriovenous malformations | |
| Diameter (cm) | 2.7 (0.7–7.9) |
| Small size | 89 (62) |
| Eloquent brain location | 66 (46) |
| Deep venous drainage | 74 (51) |
| Spetzler-Martin grade | II (I–VI) |
| Details of radiosurgery | |
| Target volume ($cm^3$) | 6.9 (0.3–24) |
| Maximal dose (Gy) | 40 (32–50) |
| Dose to margins (Gy) | 20 (15–25) |
| Follow-up period (mo) | 23 (3–72) |

Data are number (percentage) or median (range).

2009 were enrolled in this study. All patients were considered as candidates for integrating tractography, but the integration was not carried out if a target lesion was considered to be located more than 1 cm apart from these fiber tracts and risk of injuring them was considered to be sufficiently low. Malformations were located in eloquent brain areas in 66 patients (46%). Detailed treatment parameters are shown in Table 1.

Diffusion tensor magnetic resonance imaging was obtained on the day before treatment. Tractography was created from diffusion tensor imaging by using freely shared programs, according to anatomic landmarks as shown in previous studies (9–12).

On the day of treatment, patients were affixed to the stereotactic coordinate frame and underwent stereotactic magnetic resonance imaging and stereotactic cerebral angiography. Stereotactic magnetic resonance imaging and tractography were registered by using the method reported previously (9–11, 15). After the introduction of Gamma Knife 4C in October 2006, the registration process was automated (16). Tractography-integrated images were imported to treatment planning images on the day of radiosurgery. Conformal treatment planning was made by experienced neurosurgeons and radiation oncologists with use of the treatment planning software GammaPlan (Elekta Instruments AB, Stockholm, Sweden). Generally 20 Gy was given to the margin of lesions by using 40–50% isodose lines. Any portion of the anterior visual pathway and half of the brainstem were designed to receive no more than 10 Gy.

The precise location of the pyramidal tract (Fig. 1), the optic radiation (Fig. 2), or the arcuate fasciculus was confirmed on treatment planning images, and it was attempted that the maximum dose received by each fiber was less than 20 Gy, 8 Gy, or 8 Gy (20 Gy in the frontal fibers), respectively, on the basis of previous analyses (9–11), though this was not possible in some cases.

Serial formal neurologic and radiologic examination was performed every 6 months after the procedure.

## RESULTS

Diffusion tensor–based tractography was prospectively integrated in 71 (46%) of 155 treatment sessions. Integrated fiber tracts were the pyramidal tract in 45, the optic radiation in 22, and the arcuate fasciculus in 13 sessions, including 9 in which two tracts were integrated (the pyramidal tract and the optic radiation in 2, the pyramidal tract and the arcuate fasciculus in 3, the optic radiation and the arcuate fasciculus in 4). The optic radiation could not be depicted in 1 patient, and only arcuate fasciculus was drawn. Of 71 treatments with integration of tractography, the distance between the lesion and critical white matter fibers was less than 5 mm in 43 (60%); thus, tighter treatment planning was mandatory. Consequently, 39 sessions (55%) necessitated any modification in treatment planning by reducing the radiation dose to the visualized tracts. Until December 2007, 38% of treatments (37 of 98 sessions) were performed with integration of tractography, whereas tractography was integrated for 60% (34 of 57) thereafter. This difference in frequency was statistically significant according to $\chi^2$ test ($p = 0.008$).

Two patients died of unknown cause after the procedure. The other 142 patients were followed for 3–72 months (median, 23 months) after radiosurgery. During this period, transient speech disturbance was observed in 2 patients. They were treated before 2007, when we started integrating arcuate fasciculus tractography. One patient with right thalamic arteriovenous malformation showed gradual worsening of pre-existing dysesthesia of left upper and lower extremities after treatment, and this symptom lasted until the last

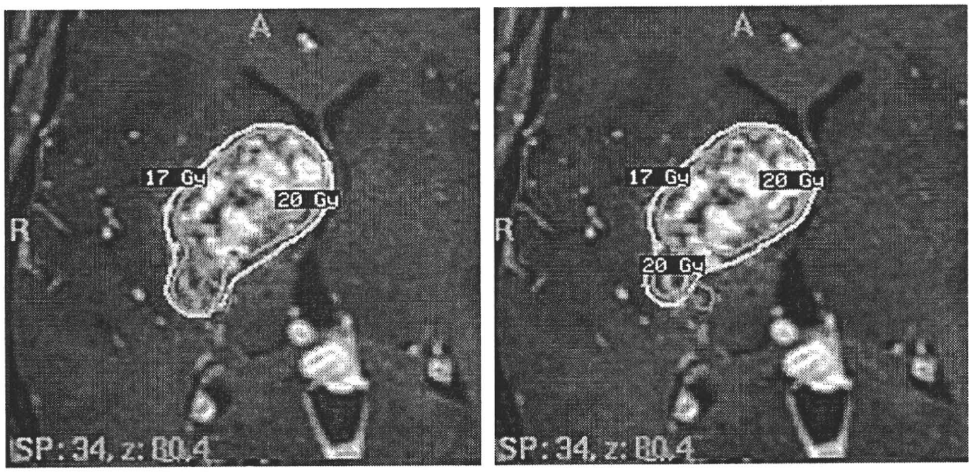


Fig. 1. Radiosurgical dosimetry of 23-year-old woman with ruptured arteriovenous malformation in the right basal ganglia. Dose delivered to the corticospinal tract before referring to tractography (a) was intentionally reduced after its integration (b).

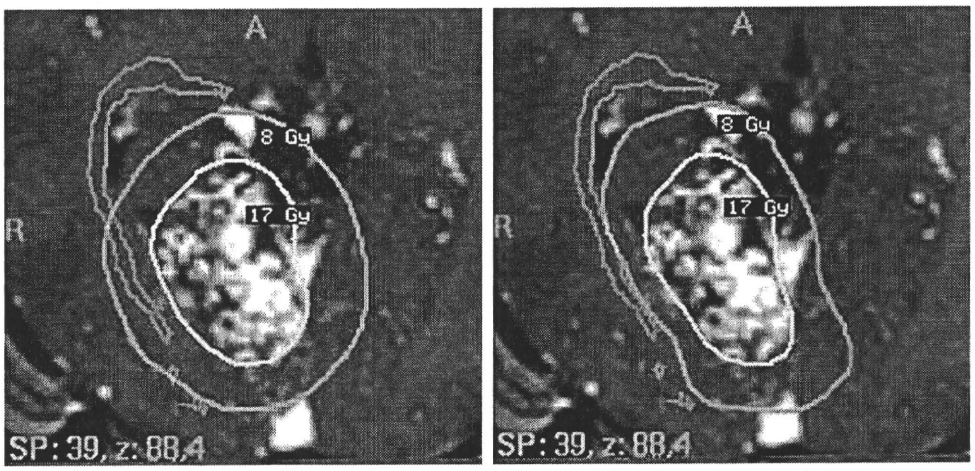


Fig. 2. Radiosurgical dosimetry of 33-year-old woman with unruptured arteriovenous malformation in the right occipital lobe. Dose delivered to the optic radiation before referring to tractography (a) was intentionally reduced after its integration (b).

follow-up at 45 months. This was the only patient who developed permanent morbidity after the prospective integration of tractography. Another patient exhibited mild transient hemiparesis 12 months after treatment prospectively integrating pyramidal tractography but fully recovered after administration of oral corticosteroid agents. Frequency of pre-existing epileptic attacks increased in 3 patients, and new onset of convulsive seizure was observed in 1 patient after radiosurgery. Nidus obliteration was confirmed by magnetic resonance imaging or angiography in 42 patients (29%) until last follow-up. Posttreatment hemorrhage was observed in 2 patients during 319 patient-years. Neither of them exhibited radiation-induced neuropathy before their subsequent hemorrhage. The other patients had no complications throughout the follow-up period.

## DISCUSSION

By integrating diffusion tensor tractography of the brain white matter to radiosurgery, permanent and transient morbidity could be reliably prevented in our patients with brain arteriovenous malformations. Although many results of utilizing diffusion tensor–based tractography for diagnostic purposes have been reported (17), its integration into treatment planning of radiosurgery is our original technique and has not been performed at any other institute. Therefore, though this is a retrospective case series, reporting our results would be the most appropriate means to evaluate its efficacy.

Although there are a variety of white matter fiber tracts, we considered that the pyramidal tract would be the most important tract in preventing morbidity of radiosurgery because its injury causes motor paresis and leads to decline of activities of daily living (18, 19). At the same time, the pyramidal tract was practically the easiest one to draw from the technical point of view (17). The optic radiation and the arcuate fasciculus would be next important and are more difficult to draw (20, 21). Injury of the optic radiation causes visual disturbance. Verbal function requires participation of a distributed neural system in the dominant hemisphere, and we integrated the arcuate fasciculus tractography to preserve this function as much as practically possible. For the time being, we are introducing the above three tracts, considering them as critical white matter structures to be preserved. Technical difficulty is also a consideration, as mentioned above. Confirming above three tracts along with anatomically identifiable critical structures of the brain would be sufficient to prevent major disabling morbidity.

Integration of tractography into intraoperative navigation was also developed at our institute (13). However, it contains risks of inevitable brain shift caused by craniotomy or tumor removal, thus leading to poorer accuracy. On the other hand, such a shift does not occur in the setting of integration of tractography into radiosurgery. Therefore, we believe this would be the most suitable clinical application of diffusion tensor tractography in treating brain disorders.

Our study has several potential limitations. Our follow-up period was not long enough to evaluate late adverse events after radiosurgery (6), although it would be appropriate to observe early radiation injury that usually occurs 6 months to 2 years after radiosurgery (2, 6). Longer follow-up would be necessary to investigate whether delayed radiation-induced neuropathy does not affect our result.

Furthermore, the obliteration rate in this study group was low, probably because the median follow-up period of 23 months was shorter than that usually necessary for nidus obliteration, which is 3–5 years (22). One concern is that obliteration on imaging or subsequent prevention of future hemorrhage, which is the therapeutic goal of radiosurgery for arteriovenous malformations, can be compromised by modification of treatment planning by referring to tractography. Therefore, we need to prove, by longer follow-up, that this technique can provide morbidity prevention without lowering the obliteration rate.

Another limitation of tractography is its reliability. There is no guarantee that fibers do not exist where the tracts is not drawn (17, 23). However, tractography has been

proven to reflect anatomic pyramidal tract functioning in intraoperative fiber stimulation analysis (24). Therefore, as indicated in this study, irradiation while paying attention to firmly depicted fibers could sufficiently prevent morbidity, and practically this is the best and the only way to prevent morbidity.

The fact that the rate of tractography integration was higher in the last 2 years suggests the feasibility and usefulness of the procedure. We hope our technique will also be applied to future treatment planning software so that even physicians who are unfamiliar with complicated imaging processing can utilize our methodology (10).

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# Long-term Outcomes of Stereotactic Radiosurgery for Arteriovenous Malformations in the Thalamus

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**BACKGROUND:** Arteriovenous malformations (AVMs) in the thalamus carry a high risk of hemorrhage. Although stereotactic radiosurgery (SRS) is widely accepted because of the high surgical morbidity and mortality of these lesions, precise long-term outcomes are largely unknown.

**OBJECTIVE:** To review our experience with SRS for thalamic AVMs based on the latest follow-up data.

**METHODS:** Forty-eight patients with thalamic AVMs were treated by SRS using the Leksell Gamma Knife and were followed. Long-term outcomes including the obliteration rate, hemorrhage after treatment, and adverse effects were retrospectively analyzed.

**RESULTS:** The annual hemorrhage rate before SRS was 14%. The mean follow-up period after SRS was 66 months (range 6-198 months). The actuarial obliteration rate confirmed by angiography was 82% at 5 years after treatment, and the annual hemorrhage rate after SRS was 0.36%. Factors associated with higher obliteration rates were previous hemorrhage ($P = .004$) and treatment using new planning software ($P = .001$). Persistent worsening of neurological symptoms was observed in 17% and more frequently seen in patients who were treated using older planning software ($P = .04$) and a higher margin dose ($P = .02$). The morbidity rate for patients who received treatment planned using new software with a margin dose not more than 20 Gy was 12%.

**CONCLUSION:** SRS for thalamic AVMs achieved a high obliteration rate and effectively decreased the risk of hemorrhage, with less morbidity compared with other modalities. Longer follow-up to evaluate the risk of delayed complications and the effort to minimize the morbidity is necessary.

**KEY WORDS:** Arteriovenous malformation, Gamma knife, Stereotactic radiosurgery, Thalamus

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Arteriovenous malformations (AVMs) in deep locations such as the thalamus frequently manifest aggressive behavior,[1-3] and drastic treatment is often needed. Despite the recent progress in microsurgical and endovascular techniques, it is still difficult to safely resect AVMs, and they still remain a therapeutic challenge.[4-7] Since its advent in the neurosurgical field, stereotactic radiosurgery (SRS) has been widely adopted in the treatment of those intractable AVMs as a safe and efficacious therapeutic modality.[8-10] According to the past literature, SRS for deeply located AVMs achieves radiographic nidus obliteration rates of 57% to 74% within 3 to 4 years, with 12% to 19% complication rates.[11-13]

**ABBREVIATIONS: AVM,** arteriovenous malformation; **SRS,** stereotactic radiosurgery

However, the precise long-term outcomes are largely unknown, especially for thalamic AVMs, including radiographic obliteration rate, risk of latency interval hemorrhage, adverse effects, and frequency of delayed neurological events. Given that AVMs are predominantly found in younger populations, it is important to verify the outcomes based on the longest follow-up data available at each time and provide the updated information for appropriate application. To address this issue, we retrospectively analyzed our experience of SRS for thalamic AVMs.

## PATIENTS AND METHODS

### Clinical Materials

Between July 1990 and March 2009, 48 patients with thalamic AVMs were treated by SRS using the

Leksell Gamma Knife (Elekta Instruments AB, Stockholm, Sweden) at our institution. In all patients, diagnosis was confirmed with cerebral angiography in combination with computed tomography or magnetic resonance imaging (MRI). Four patients (8%) had been initially treated with other modalities (surgical resection in 2, endovascular treatment in 1, and surgical resection with endovascular treatment in 1) and were referred to our hospital for SRS of the residual nidus. In the other 44 patients (92%), SRS was the primary treatment. The radiosurgery-based grading system scores (AVM scores) proposed by Pollock and Flickinger[14] was also used to evaluate the patient outcomes, calculated according to the following equation in thalamic AVMs: 0.1 × AVM volume (in $cm^3$) + 0.02 × patient age (in years) + 0.3 × 2.

### Radiosurgical Treatment

After the Leksell stereotactic frame was fixed on the patient's head, he or she underwent stereotactic imaging to obtain precise information on the shape, volume, and 3-dimensional coordinates of the AVM nidus. Biplanar stereotactic cerebral angiography was solely used for radiosurgical dose planning until February 1991. Thereafter, computed tomography or MRI was used in combination with angiography. Treatment planning was jointly performed by neurosurgeons and radiation oncologists using commercially available software. The first-generation treatment planning software (KULA; Elekta Instruments AB), with which prescribed dose planning was manually superimposed on radiographic imaging films, was used until September 1998. Advanced planning software (Leksell GammaPlan; Elekta Instruments AB) that enabled the display of multiple radiographic images on the computer screen and simultaneously superimposed isodose lines on them was used thereafter. In principle, the ideal dose applied to the margin of each AVM nidus was 20 Gy or greater. The prescription dose was occasionally reduced because of the nidus volume, the location of AVMs near the critical anatomy, or the clinical status of the patients.

### Follow-up Evaluation and Statistical Analysis

After SRS, follow-up clinical examinations were performed at our hospital or by referring physicians. Serial cerebral angiography was performed every year until 1992. After 1993, the patients underwent computed tomography or MRI with contrast enhancement every 6 months, and angiography was performed when obliteration of the AVM nidus was strongly suggested on those images.

The actuarial obliteration rate was calculated using the Kaplan-Meier method. The Cox proportional hazard model was used for multivariate analyses for evaluating factors potentially affecting nidus obliteration and adverse effects. The Fisher exact test was used to compare the ratio of the patients who experienced complete nidus obliteration without any deficit.

## RESULTS

### Patients, Characteristics of Lesions, and Treatment

The clinical characteristics are summarized in Table 1. Forty-eight patients were followed for 6 to 198 months (mean 66 months, median 45 months) after SRS. Among them, 43 patients were followed for more than 1 year. The patient age at the time of SRS ranged from 5 to 58 years (mean 25 years, median 23 years). When graded using the Spetzler-Martin classification,[15] 39 (81%) were grade III and 9 (19%) were grade IV. The mean nidus volume was 3.3 $cm^3$ (range 0.1-18 $cm^3$). The mean radiosurgery-based AVM score was 1.40 (range 0.84-2.49). Forty-two patients (88%) experienced 59 hemorrhages before SRS. The period between the last hemorrhages before SRS and the time of SRS was 1 to 146 months (mean 15 months, median 6 months. Between the time of diagnosis and SRS, excluding the first bleedings in patients who presented with hemorrhage, 15 hemorrhages were observed

**TABLE 1. Clinical Characteristics and Radiosurgical Dosimetry for Patients With Thalamic AVMs[a]**

| Characteristics | Value |
|---|---|
| No. of patients in analysis | 48 |
| M/F ratio | 23/25 |
| Age, y | |
| *Range* | 5-58 |
| *Mean* | 25 |
| *Median* | 23 |
| Clinical presentation, no. (%) | |
| *Hemorrhage* | 42 (88) |
| *Headache* | 1 (2) |
| *Incidental* | 5 (10) |
| Neurological deficit, no. (%) | |
| *No deficit* | 14 (29) |
| *Motor deficit* | 22 (46) |
| *Sensory disturbance* | 19 (40) |
| *Visual disturbance* | 6 (13) |
| *Aphasia* | 3 (6) |
| Spetzler-Martin grade, no. (%) | |
| *III* | 39 (81) |
| *IV* | 9 (19) |
| Radiosurgery-based AVM score | |
| *Range* | 0.84-2.49 |
| *Mean* | 1.40 |
| *Median* | 1.33 |
| Previous treatment, no. (%) | |
| *No previous treatment* | 44 (92) |
| *Endovascular embolization* | 2 (4) |
| *Microsurgical resection* | 3 (6) |
| Radiosurgical dosimetry | |
| *Maximum dose, Gy* | |
| Range | 27-50 |
| Mean | 40 |
| Median | 40 |
| *Margin dose, Gy* | |
| Range | 16-28 |
| Mean | 21 |
| Median | 20 |

[a] AVM, arteriovenous malformation.

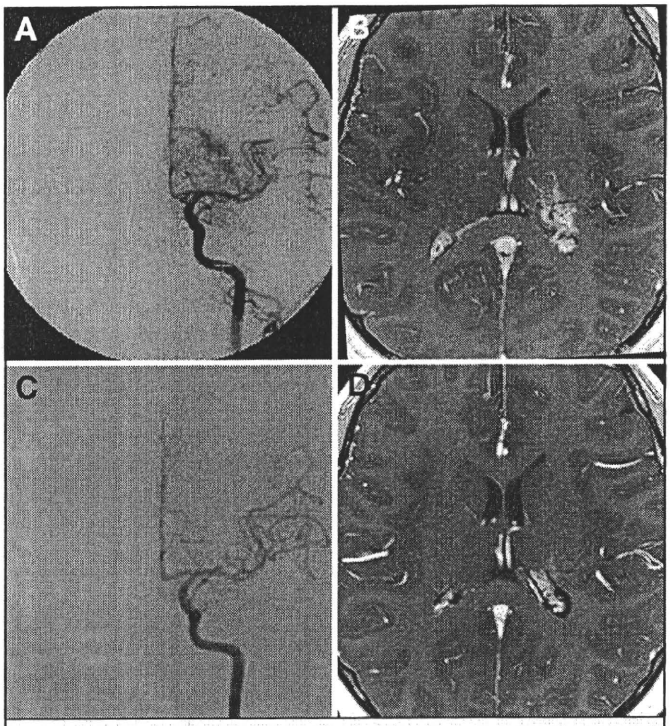


**FIGURE 1.** *A, pretreatment angiography and magnetization prepared rapid gradient echo sequence (MPRAGE) of magnetic resonance imaging (**B**) of an arteriovenous malformation in the left thalamus presenting with repeated hemorrhage. Nidus obliteration without complications was confirmed 28 months after stereotactic radiosurgery by angiography (**C**) and MPRAGE (**D**).*

during 107 person-years. By the person-years method, the annual hemorrhage rate after initial presentation until SRS was 14%. If the annual bleeding rate was calculated based on all the hemorrhages during a whole lifetime, it could be estimated as 4.9%. At the time of SRS, 34 patients (71%) demonstrated neurological deficits caused by past hemorrhage or as complications of the previous treatment; 22 (46%) presented with motor weakness, 19 (40%) with sensory disturbance, 6 (13%) with visual field loss, and 3 (6%) with aphasia. For SRS using the gamma knife, the maximal dose ranged from 27 to 50 Gy (mean 40 Gy, median 40 Gy) and the marginal dose ranged from 16 to 28 Gy (mean 21 Gy, median 20 Gy).

## Obliteration Rate

Complete nidus obliteration (Figure 1) was confirmed by angiography in 31 patients (65%) within 12 to 64 months (median 25 months) after SRS. Four patients (9%) underwent a second SRS for residual nidus, and complete obliteration was confirmed in these patients 12 to 53 months after the second treatments. The actuarial rates of AVM obliteration confirmed by angiography were 67% at 3 years and 82% at 5 years. There were 2 cases in which MRI demonstrated complete obliteration of the AVM nidus without angiographic confirmation. When these cases are counted as having complete obliteration of the nidus, the obliteration rates

**TABLE 2. Factors Associated With Angiographically Confirmed Obliteration of the AVM Nidus After Stereotactic Radiosurgery[a]**

| Factor | *P* Value | |
|---|---|---|
| | Univariate | Multivariate |
| Age | .87 | .41 |
| Sex | .70 | .84 |
| Hemorrhage before treatment | .91 | .004[b] |
| Nidus fed by | | |
| *Anterior choroidal artery* | .90 | .71 |
| *Lenticulostriate artery* | .61 | .40 |
| *Posterior choroidal artery* | .21 | .06 |
| *Thalamogeniculate artery* | .08 | .06 |
| *Nidus volume* | .06 | .11 |
| *AVM score* | .06 | |
| *Spetzler-Martin grading* | .17 | .53 |
| *Use of GammaPlan* | .11 | .001[b] |
| *Use of CT or MRI* | .76 | .22 |
| *Maximum dose* | .28 | .52 |
| *Margin dose* | .09 | .25 |

[a] AVM, arteriovenous malformation; CT, computed tomography; MRI, magnetic resonance imaging.
[b] $P < .05$.

were 72% at 3 years and 85% and 5 years. Additionally, among 43 patients who were observed for more than 1 year, 24 patients (56%) experienced complete nidus obliteration without any deficit. Complete nidus obliteration without new deficit was achieved in 13 (68%) of 19 patients with AVM scores lower than 1.3 and in 11 (48%) of 23 patients with AVM scores higher than 1.3 ($P$ = .22), although this outcome was not statistically significant.

Factors significantly associated with higher obliteration rates in the multivariate analysis were previous hemorrhage ($P$ = .004) and treatment using a new planning software ($P$ = .001) (Table 2).

## Complications and Hemorrhagic Events

T2 hyperintensity regions around the irradiated field confirmed by MRI developed in 12 patients (25%) 10 to 21 months (median 12 months) after SRS. Neurological deterioration was observed in 10 patients (21%) 1 to 21 months (median 11 months) after SRS. In 2 patients, symptoms were transient dysesthesia and lasted 3 and 38 months, respectively. Eight patients (17%) had persistent symptoms, of whom 5 patients experienced newly developed neurological deficits (sensory disturbance in 2, motor deficit in 2, and quadrant hemianopsia in 1), and worsening of existing neurological symptoms was found in 3 patients (sensory disturbance in 2, motor deficit in 1).

Factors affecting neurological deterioration after SRS in the multivariate analysis were higher margin dose ($P$ = .02), treatment using the first-generation dose planning system ($P$ = .04),

**TABLE 3. Factors Associated With Neurological Deterioration After Stereotactic Radiosurgery[a]**

| Factor | *P* Value | |
|---|---|---|
| | Univariate | Multivariate |
| Age | .58 | .42 |
| Sex | .56 | .84 |
| Nidus fed by | | |
| *Anterior choroidal artery* | .52 | .68 |
| *Lenticulostriate artery* | .59 | .30 |
| *Posterior choroidal artery* | .06 | .09 |
| *Thalamogeniculate artery* | .11 | .04[b] |
| *Nidus volume* | .32 | .27 |
| *AVM score* | .22 | |
| *Spetzler-Martin grading* | .42 | .84 |
| *Use of KULA* | .05 | .04 |
| *Use of CT or MRI* | .75 | .99 |
| *Maximum dose* | .41 | .15 |
| *Margin dose* | .54 | .02[b] |

[a] AVM, arteriovenous malformation; CT, computed tomography; MRI, magnetic resonance imaging.
[b] $P < .05$.

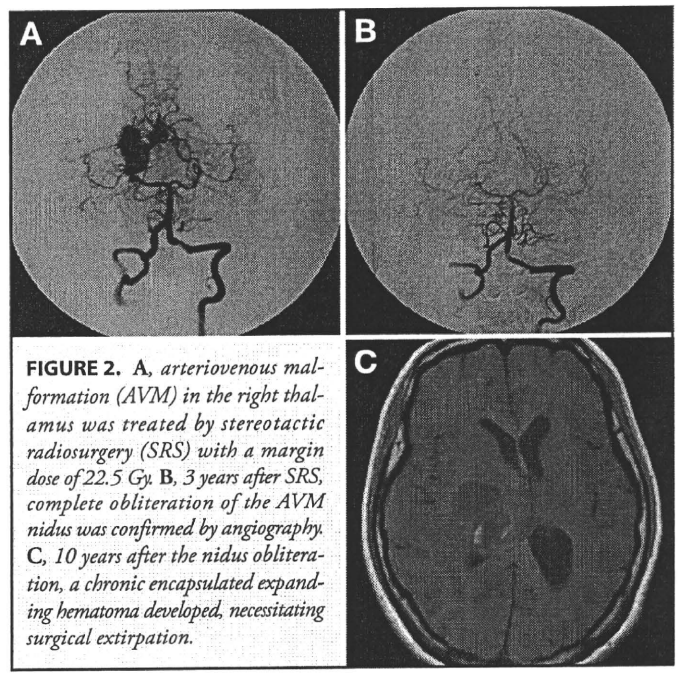


**FIGURE 2. A,** *arteriovenous malformation (AVM) in the right thalamus was treated by stereotactic radiosurgery (SRS) with a margin dose of 22.5 Gy.* **B,** *3 years after SRS, complete obliteration of the AVM nidus was confirmed by angiography.* **C,** *10 years after the nidus obliteration, a chronic encapsulated expanding hematoma developed, necessitating surgical extirpation.*

and the nidus fed by the thalamogeniculate artery ($P = .04$) (Table 3). Seventeen patients underwent treatment planned by new planning software with the margin dose not more than 20 Gy. Among those patients, 1 experienced persistent visual field loss and another patient presented worsening of sensory disturbance. Therefore, the rate of permanent adverse effects for this group of patients was 12%, whereas the obliteration rates were 64% and 82% at 3 and 5 years after SRS, respectively, which were not significantly different ($P = .37$) compared with patients who underwent treatment with old software or with margin doses more than 20 Gy.

There was no latency interval hemorrhage after SRS in this cohort during 275 patient-years. In 1 patient, a chronic encapsulated expanding hematoma developed 10 years after nidus obliteration (Figure 2). As the hematoma progressively enlarged and her consciousness gradually deteriorated, surgical removal of the lesion was performed. Counting this as a hemorrhagic event, the annual risk of hemorrhage after SRS was 0.36%.

## DISCUSSION

Deep-seated AVMs are more likely to cause devastating hemorrhage.[1-3,16,17] In AVMs located in the basal ganglia and thalamus, the annual rates of bleeding were reported to be 9.8% to 11.4%, which is in line with the hemorrhage rate in our patients. Because the risk of morbidity and mortality is high,[9,11,18] earlier extirpation is desirable before repeated hemorrhages. For this purpose, microsurgical resection can be a preferable treatment option. However, with surgery for thalamic AVMs, neurological deterioration is frequently inevitable because of the proximity to critical anatomic structures, which is a main reason to for not choosing this therapeutic option.[17] At our institution, we have been striving to treat those intractable AVMs and have reported outcomes of various treatment modalities including microsurgery, endovascular treatment, and SRS.[17,19,20] In our experience, microsurgical resection with preoperative embolization and intraoperative electrophysiological monitoring warrants acceptably low complication rates in the small AVMs, especially when accompanied with hematomas.[17] Therefore, even with challenging AVMs, microsurgery can be the first-line of treatment in selected patients during the acute phase of the disease. SRS contributed to markedly reducing the risks of mortality and morbidity not only in the patients with surgically intractable small AVMs but also in those without severe neurological deficits who had been observed conservatively before the advent of this option.[17] In the previous literature reporting the outcomes of SRS for AVMs in the thalamus and basal ganglia, the nidus obliteration rates were 45% to 62% at 3 years, and the obliteration rates without neurological complications were 39% to 55%.[12,13] We followed patients longer than patients in those reports were followed and achieved 82% of the nidus obliteration rate at 5 years, and the nidus obliteration rate without neurological complications reached 56%, which indicated the efficacy of SRS for these lesions. On the other hand, the morbidity rates were reported as 12% to 19%, higher than those of AVMs in other parts of the brain, which is 2.7% to 8%.[19,21-23] In our study, 0% mortality rate was achieved for the last follow-up period, but the associated morbidity rate was 17%, which was not negligible. Those results indicated that, compared with the outcomes of other treatment

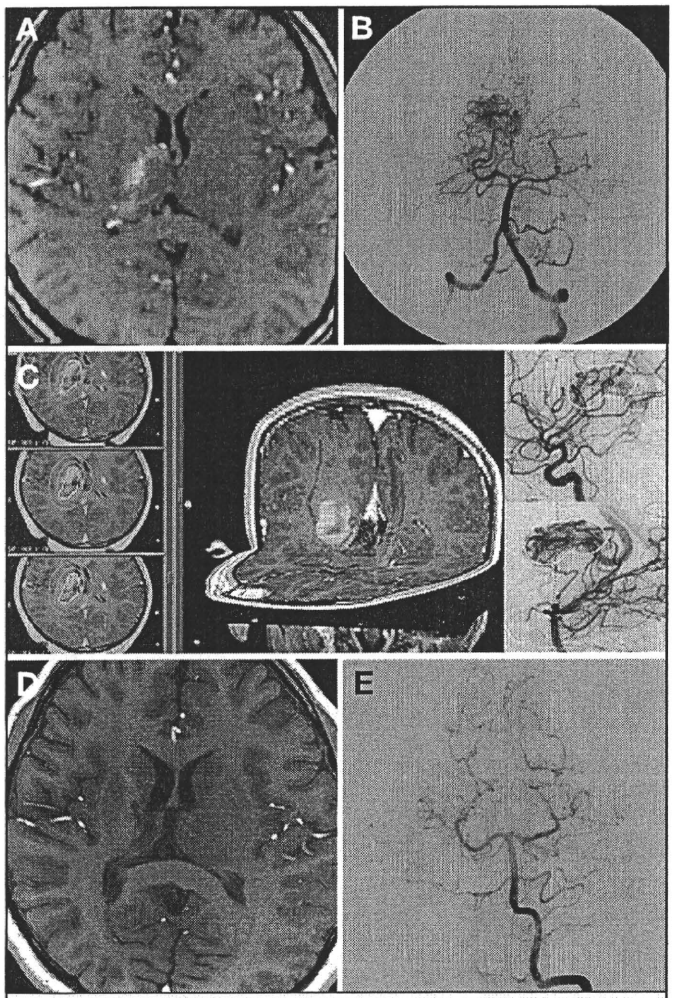


**FIGURE 3.** *Pretreatment magnetization prepared rapid gradient echo sequence (MPRAGE) of magnetic resonance imaging (***A***) and angiography (***B***) of an arteriovenous malformation (AVM) in the right thalamus.* **C**, *the lesion was treated by stereotactic radiosurgery (SRS) with integration of diffusion-tensor tractography. Nidus obliteration without complications was demonstrated 3 years after SRS by MPRAGE (***D***) and angiography (***E***).*

modalities, SRS can be an acceptable treatment modality for thalamic AVMs at present. However, at the same time they suggested the necessity of strenuous efforts to reduce the complications associated with SRS. The lower rate of adverse effects in the group of patients who underwent treatment guided by new planning software suggested that technical advancement would play an important role in making SRS safer. In January 2006, we started to modify treatment planning, so integrated tractography was kept outside the 20-Gy isodose line as much as possible, whereas the delivered dose to the margin of the nidus was not reduced to less than 20 Gy[24,25] (Figure 3). Although further follow-up and accumulation of the cases are still necessary to legitimately evaluate the efficacy of this method, improvement of the morbidity rate associated with SRS will be expected.

Delayed complications such as hemorrhage from obliterated AVMs, chronic encapsulated expanding hematoma, and delayed cyst formation can occur even more than 10 years after the treatment,[18,26] and it is still premature to evaluate the incidence. At present, those complications are reported as relatively rare phenomena, but the cumulative risk might be much higher in young patients with long lives ahead of them. Therefore, continued follow-up is recommended even after AVM obliteration has been demonstrated on angiography, and in thalamic AVMs, once there is a developing hematoma, we advocate surgical resection of the obliterated nidus before the patient experiences serious neurological deterioration.

The limitations of this study include limited reliability of multivariate analyses owing to the relatively small number of patients, although the results obtained were similar to the results of our previous study[19] and unpublished data in which larger number of patients with cerebral AVMs were analyzed. We present the outcomes of SRS for thalamic AVMs based on our maximum follow-up data, but SRS is a relatively new treatment modality and our knowledge of its long-term risks is still limited. From the standpoint of a "sufficiently long-term outcome," we have still not reached the midway point of the long journey.

## CONCLUSION

Based on the long-term follow-up data, we consider SRS to be acceptable as an alternative treatment for small thalamic AVMs in which a sufficient obliteration rate is achieved with lower risks of hemorrhage occurring during the latency period. The rate of neurological complications is still high, reflecting proximity to vital structures, but is expected to improve in the future with advancement of technologies. The incidence and risk of delayed complications are still not clear, and we should continue to observe patients carefully, even after obliteration has been confirmed by angiography after SRS.

### Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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## COMMENTS

Patients with arteriovenous malformations (AVMs) in deep brain locations carry a high risk for both observation and treatment. The majority of these patients are diagnosed only after an intracranial hemorrhage with a high percentage having a neurologic deficit secondary to their bleed. Unlike hemispheric or cerebellar AVMs, most neurosurgeons consider the risk of resection prohibitive unless the patient already has a significant sensorimotor deficit, and even then, few cerebrovascular neurosurgeons seriously contemplate resection of AVMs involving the basal ganglia, thalamus, or brainstem. Consequently, radiosurgery has become the preferred management for virtually all patients with these difficult lesions. In this study, Koga et al have carefully analyzed the outcomes of 48 patients having radiosurgery for thalamic AVMs. At a mean follow-up interval of 66 months, complete nidus obliteration without new neurologic deficits was achieved by 56 percent of patients after one or more radiosurgical procedures. Utilization of newer software for radiosurgical dose planning was associated with more frequent obliteration and a lower risk of radiation-related complications when compared to older dose planning platforms. Also, at prescribed doses greater than 20 Gy, the obliteration rate was not improved, but more patients developed new permanent neurologic deficits. Although the observed morbidity rate of 12 percent for recently treated patients receiving 20 Gy or less as recommended by the authors' remains significant, it is far less than the predicted morbidity of observation for these primarily young patients (median age, 23 years).

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Koga et al carefully analyzed the outcome of radiosurgery in 48 patients with thalamic AVM. Their pretreatment post-diagnosis hemorrhage rate of 14% (not counting patients who present with bleeding) might be slightly elevated by some selection bias but nevertheless illustrates the severity of the problem that they seed to address with radiosurgery. Their morbidity rate (transient or permanent) of 12% in recent patients treated to doses no greater than 20 Gy is not significantly greater than most large AVM radiosurgery series including all locations. They did not compare the risk of permanent neurological injury in the thalamus with other locations. Permanent neurological morbidity does seem to be more likely in the thalamus and other deep structures compared to lower risk regions like the frontal or temporal lobes, where most of the complications tend to be transient headaches or seizures. Nevertheless, radiosurgery is the best management strategy for thalamic AVMs in patients whose expected risk of hemorrhage in their remaining lifespan exceeds that 12% risk of morbidity from the procedure.

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DISEASES OF THE ESOPHAGUS

Original article

# Esophageal cancer: definitive chemoradiotherapy for elderly patients

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*SUMMARY.* **To investigate the efficacy and toxicity of definitive chemoradiotherapy (CRT) for elderly patients with locally advanced esophageal cancer. Twenty-two patients aged over 75 that performed definitive CRT were retrospectively reviewed. The regimen included concurrent CRT consisting of two cycles of chemotherapy (CTx) of platinum and 5-fluorouracil, and radiation therapy (RT) of 50–50.4 Gy (actual range: 45.4–71.4 Gy), and additional CTx where possible. Both CTx and RT were reduced in dose and field where necessary. The disease-free survival rate and the overall survival rate at 3 years were 33.3% ± 11.4% and 25.9% ± 10.8%. Grade 4 leukocytopenia and thrombocytopenia occurred in three (14%) and four (18%) patients. Treatment-related death was suspected in up to four (18%) patients at the most. Univariate analyses for disease-free survival showed that neither total radiation dose nor number of total cycles of CTx was significant. The pattern of relapse was predominantly more frequent in the intra-RT field than outside the RT field. For elderly patients, adverse events are frequent, and decreased organ reserve may cause treatment-related death. Reduction in CTx dose or RT field, appropriate only for two cycles of CTx, and careful monitoring may help to minimize toxicity. Physicians should not be too afraid of adverse events or be negative about CRT for elderly patients, as long as comorbidities and complications are managed carefully.**

*KEY WORDS*: **chemoradiotherapy, chemotherapy, elderly patient, esophageal cancer, radiotherapy.**

## INTRODUCTION

Continual great advances in a broad range of fields, including medical care, social welfare, and elderly care, have resulted in an aging society in Japan. According to the 20th Life Tables in 2005 in Japan, the life expectancy was 78.56 and 85.52 for men and women, respectively, which has increased year after year.[1]

Esophageal cancer is one of the most aggressive cancers, with a 5-year survival rate of 25.0 ± 0.6%.[2] It occurs mainly in the middle aged and elderly. In 2004, the total incidence of esophageal cancer in the Japanese population was 17 815, of which the incidence in patients over the age of 75 was 4964 (28%).[3]

Up until now, surgery has been considered to be the mainstay treatment for locally advanced resectable esophageal cancer. However, it is clear that a combined modality therapy such as chemoradiotherapy (CRT) is also the key to successful treatment. Although elderly patients may often be unfit for surgery because of comorbidities or decreased organ reserve, recent improvements in surgical techniques and postoperative management provide safely esophagectomy, and now, it is not a contraindication for elderly patients. However, to gain a long-term definitive cure from radical surgical resection alone is difficult, and surgery-related reduction in quality of life is significant. Thus, definitive CRT, radiation therapy (RT) alone, or chemotherapy (CTx) alone must be considered for all patients. Today, it is most important to determine therapeutic strategy itself among various choices based on the concept of informed consent even in elderly patients. Nevertheless, in reality, many physicians are hesitant to deliver aggressive treatment to elderly patients because of severe toxicity. There have been a few reports on the use of definitive CRT for elderly patients with esophageal cancer,[4–9] and the appropriate dose intensity and method remain controversial.

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A previous study demonstrated that elderly patients have poor treatment compliance on CRT, resulting in a decreased survival rate as compared with non-elderly patients.[4] Meanwhile, Uno *et al.* revealed that old age by itself is not an adequate reason to exclude patients from aggressive treatment,[5] and some reports have also showed that definitive CRT in elderly patients was effective without a major increase in adverse events.[6–9] Nevertheless, it is not obvious how unfavorable or significant the effects of old age itself on treatment schedule and treatment course are.

Today, life expectancy keeps on increasing, and against such a background, it must be recognized that elderly patients do not necessarily have only a short time left to live. They could be given great and invaluable benefits if aggressive treatment could succeed in increasing their lifetime, which would be a just advantage from medical progress.

The aim of this study was to investigate retrospectively the efficacy and toxicity of definitive CRT for elderly patients aged 75 and older with locally advanced esophageal cancer.

## MATERIALS AND METHODS

### Patients

Between December 2003 and August 2008, 105 consecutive patients with newly diagnosed locally advanced esophageal cancer underwent definitive CRT at the University of Tokyo Hospital. Of these patients, 22 (21%) patients aged over 75 years were retrospectively reviewed. The main reasons for indication of CRT and/or contraindication of surgery were rejection of surgery ($n = 7$) or no indication of surgery because of advanced age ($n = 6$), lower performance status (PS) ($n = 3$), severe comorbidity ($n = 4$), or tumor location (cervical esophagus) ($n = 2$).

Selection for definitive CRT included the following criteria, which were met by all 22 patients: (i) histologically confirmed squamous cell carcinoma (SqCC) or adenocarcinoma; (ii) clinical stages I to IV disease according to the American Joint Committee on Cancer TNM classification on malignant tumors, 1983, except for stage IVb disease because of distant and hematogenous visceral metastasis (if a stage IVb was because of lymph node metastases that could be potentially covered in the same radiation fields, it was eligible); (iii) Karnofsky Performance Status (KPS) of at least 70%; (iv) no evidence of severe comorbidities or organ dysfunction; (v) adequate bone marrow, renal, hepatic, cardiac, and respiratory function (white blood cell >3000/μL, platelet >10 × $10^4$/μL, serum creatinine <1.5 mg/dL); and (vi) no severe interstitial pneumonia (no interstitial pneumonia shadow on computed tomography [CT]). Prior therapy for esophageal cancer except for endoscopic mucosal resection and endoscopic submucosal dissection was ineligible. Although other severe malignant neoplasm was ineligible, that of controllable state was selected. There were two patients with other malignant neoplasms: one with hepatocellular carcinoma and another one with advanced stomach cancer (cT3N2M0) with partial response for CTx using paclitaxel and TS-1, tegafur, gimeracil, and oteracil potassium at the start of CRT for esophageal cancer.

### Pretreatment evaluation

All patients were clinically evaluated for their pretreatment state by physical examination; biopsy of primary tumor; endoscopy of the upper gastrointestinal tract; CT of neck, chest, and abdomen; complete blood cell count; and biochemistry evaluation. Some optional examinations were carried out as follows: esophagography for 19 patients (86%) and [18F] fluoro-2-deoxy-D-glucose positron emission tomography for 18 patients (82%). Endoscopic ultrasonography and bronchoscopy were done only if considered necessary. All patients were assigned to a clinical stage on the basis of the American Joint Committee on Cancer TNM classification, 1983.

### Treatment schedule

CTx was administered concurrently with RT, starting on day 1.

*CTx*

Platinum-based CTx, combined with 5-fluorouracil (5-FU), was given to all patients. Before 2006, cisplatin (CDDP) was used mainly as the platinum anticancer drug. After recommendation of its efficacy and safety, nedaplatin (NDP) instead of CDDP has been frequently used with 5-FU, and since 2006, it has become the standard CTx regimen at this institution regardless of renal dysfunction.[10–13] CDDP (75 mg/$m^2$) or NDP (80 mg/$m^2$) was administered intravenously on day 1 of each cycle, and 5-FU (1000 mg/$m^2$/day or 800 mg/$m^2$/day) was administered as a continuous intravenous infusion on days 1–4 of each cycle with standard premedication. This cycle of CTx was repeated with an interval of 4 weeks, and a total of three to four cycles were delivered where possible, which represented that this schedule was composed of concurrent CRT phase (first and second cycle of CTx) and adjuvant CTx phase. Several risks such as advanced age, lower PS, or renal dysfunction required a reduction in dose ($n = 11$ [50%] in this study). At the start of the second cycle, both white blood cell and platelet count had to be elevated at >2500/μL and >10 × $10^4$/μL, respectively, and renal function had to be returned to normal. If these

criteria were not satisfied, CTx was suspended, discontinued, or given at a reduced dose.

*RT*

A linear accelerator of 6 MV or 10 MV was used. For all patients, the radiation field consisted of the four-portal approach: anterior and posterior opposed portals and two lateral oblique off-cord opposed portals positioned by three-dimensional CT planning in order to avoid a high dose to the spinal cord. In some cases, multiple (>4) portals were used in the field-in-field method to make the dose distribution within the planning target volume homogeneous (95–107% of the prescription dose). All fields were delivered every day, and the daily fractional dose was 1.8–2.0 Gy, administered 5 days a week, up to a total dose of 50–50.4 Gy. For patients aged less than 80 years, an extended field, consisting of gross tumor volume plus the thoracic and abdominal esophagus and M1a region, was irradiated where possible. This meant that cases in which the primary location was the cervical or upper thoracic esophagus could be treated by a so-called T-shape field, which included the bilateral supraclavicular lymph node areas. For patients with an advanced age of 80 years, an involved field including gross tumor volume plus a margin of 1.5 cm laterally and 3–5 cm cranio-caudally was used. Evaluation was performed by using a dose volume histogram as follows: The maximum dose to the spinal cord was limited to 50 Gy, the $V_{20}$ of the lung was limited to <20%, and the mean dose to the lung was limited to 10 Gy.

### Analysis of response and statistics

StatView Dataset File Version 5.0 J for Windows (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. Survival periods were calculated from the start of irradiation to either the date of death or the latest follow-up date. Disease-free survival (DFS) was calculated from the start of irradiation to the date of death, to the last follow-up date, or to the clearance of relapse by radiographic or endoscopic modality. Survival curves were estimated with the Kaplan–Meier method estimator, and log-rank tests were used to compare the survival distributions. Univariate analysis and further multivariate analysis were demonstrated by a log-rank test and Cox regression analysis. The World Health Organization response criteria for measurable lesions were used to determine the tumor response.[14] Toxicity was assessed and documented according to Common Terminology Criteria for Adverse Events version 3.0. Differences with values of $P < 0.05$ were considered statistically significant.

## RESULTS

All 22 patients were followed until death or time of analysis. The last follow-up was performed on April 30, 2009. Six of the 22 patients (27%) were alive, consisting of five patients in a disease-free state and one patient with relapse. The median follow-up period for surviving patients was 23.8 months (range: 8.3–53.6 months).

### Patient and tumor characteristics

Patient and tumor characteristics are shown in Table 1. Nineteen males and three females were included in the analysis. The median age was 79 years (range: 75–85 years). The middle thoracic esophagus was the most frequent primary location, occurring in 10 patients (46%). The most frequent tumor stage was T3, which was observed in 13 patients. N1 disease was observed in 14 patients. Only one patient had M1b (LYM) disease. All cases were SqCC. The most frequent number of total cycles of CTx was two ($n = 10$), and the most frequent total dose of RT was 50.4 Gy

**Table 1** Patient and tumor characteristics

| Factor | No. |
|---|---|
| Age | |
| Median (range) | 79 (75–85) |
| Sex | |
| Male : female | 19 : 3 |
| Location | |
| Ce : Ut : Mt : Lt | 2 : 4 : 10 : 6 |
| Tumor stage | |
| T1 : T2 : T3 : T4 | 3 : 4 : 13 : 2 |
| Nodal stage | |
| N0 : N1 | 8 : 14 |
| Metastatic stage | |
| M0 : M1a : M1b | 21 : 0 : 1 |
| TNM stage | |
| I : II : III : IV | 3 : 6 : 12 : 1 |
| KPS | |
| ≥90% : <90% | 12 : 10 |
| SUV max of primary | |
| <5 : ≥5 | 3 : 15 |
| Tumor length | |
| <5 cm : 5–<10 cm : ≤10 cm | 5 : 14 : 3 |
| CTx regimen | |
| CDDP group : NDP group | 5 : 17 |
| Reduction in dose of CTx at the first cycle | |
| 100% : 80% : 70% : 66% | 11 : 7 : 3 : 1 |
| Radiation dose | |
| 50–50.4 Gy : the others | 17 : 5 |
| Serum SCC in pretreatment | |
| High : WNL | 13 : 9 |
| Serum CYFRA in pretreatment | |
| High : WNL | 3 : 19 |
| Serum CEA in pretreatment | |
| High : WNL | 7 : 15 |

SUV max were available for 18 patients. CDDP, cisplatin; Ce, cervical; CEA, carcinoembryonic antigen; CTx, chemotherapy; CYFRA, cytokeratin 19 fragment marker; KPS, Karnofsky Performance Status; Lt, lower thoracic; Mt, middle thoracic; NDP, nedaplatin; SCC, squamous cell carcinoma antigen; SUV max, maximum standardized uptake value; Ut, upper thoracic; WNL, within normal limit.