Table 1 Patient characteristics

Age (range) (years)	57 (17–84)
Gender (male/female)	52/38
Primary site	
Maxillary sinus	12
Ethmoid sinus	8
Sphenoid sinus	5
Nasal cavity	62
Other site	3
Tumor type	
Squamous cell carcinoma	22
Adenoid cystic carcinoma	15
Olfactory neuroblastoma	27
Melanoma	14
Others	12
TNM stage	
T	
T1	4
T2	16
T3	9
T4	54
Tx	7
N	
N0	88
N1[a]	3
N2	0
PBT dose schedule ($BED_{3.0}$)	
70 GyE/28 fr (128.3 Gy)	5
70 GyE/35 fr (116.7 Gy)	4
66 Gy/33 fr (110 Gy)	1
65 GyE/26 fr (119.2 Gy)	61
60 GyE/15 fr (140 Gy)	14
60 GyE<	5

fr Fraction, *PBT* proton beam therapy, *BED* biological equivalent dose

[a] All lymph node metastases had located nearby primary tumor.

time was censored at the last confirmed date of survival if the patient was alive. Progression-free survival time was defined from the start of treatment to the first day of confirmation of progressive disease at any site or any cause of death.

Results

Patient characteristics

A total of 112 patients with malignancies of the nasal cavity, paranasal sinuses, or involving the skull base were treated using PBT. For 10 patients, the follow-up duration was 1 year or less, mainly because patients were referred to our institution from hospitals or institutions located far from our institution. Another 12 patients died within 1 year after PBT. Therefore, as for late toxicities, the remaining 90 patients were reviewed in the current study.

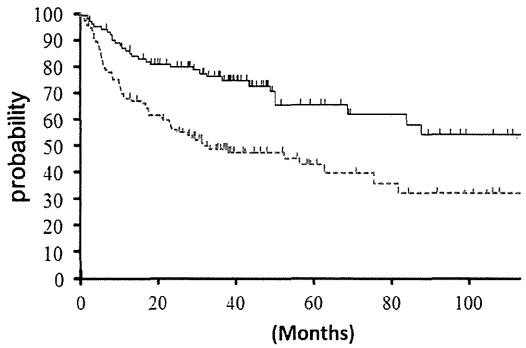

Fig. 1 Overall and progression-free survival for all the 112 patients. *Solid line* indicates overall survival curve; *broken line* indicates progression-free survival curve. With a median follow-up period of 57.5 months, 3-year overall survival and progression-free survival rates were 74.7 % and 48.2 %, respectively, and the 5-year overall and progression-free rates were 64.2 % and 44.5 %, respectively

Median age was 57 years (range, 17–84 years). The major primary site was the nasal cavity ($n = 62$, 69 %). Regarding treatment, 16 patients received surgery before PBT, and 20 patients received induction chemotherapy before PBT. Eleven patients received PBT concurrently with cisplatin, and the remaining patients received PBT alone.

The most common treatment was PBT alone at 65 GyE in 26 fractions. Patient characteristics are listed in Table 1.

Treatment outcome

Median observation period was 57.5 months (range, 12.4–162.7 months). Among 112 patients, the 5-year progression-free and overall survival rates were 44.5 % and 64.2 %, respectively (Fig. 1). A total of 55 patients were confirmed to have tumor progression, consisting of 26, 14, and 15 patients with local, regional, and distant failure, respectively. Eleven patients had not visited for more than 2 years, and we were unable to confirm death. Of these 11, recurrence could not be confirmed in 7 patients.

Late toxicity profile

The toxicity profile is listed in Table 2. Median time to onset of grade 2 or greater late toxicity, except cataract, was 39.2 months (range, 2.7–99.8 months), and 3 patients developed grade 2 or more severe toxicities; the interval from the completion of PBT was more than 5 years. Grade 3 late toxicities occurred in 17 patients (19 %) with 19 events. Grade 3 osteonecrosis caused by exodontia after

Table 2 Late toxicity ($n = 90$)

Grade (CTCAE version 4.0)	1	2	3	4
Hearing loss	1	1	2	0
Nerve disorder[a]	0	1	1	0
Encephalomyelitis infection	0	0	0	2
Cataract	1	1	5	0
Optic nerve disorder	0	4	1	4
Necrosis (other, specify)[b]				
Brain	5	1	1	0
Soft tissue	0	0	1	0
Bone	0	4	2	0

[a] All central nervous system disorders (I–XII) were classified in this category

[b] In-field necrosis induced by PBT was classified in the nearest implication of CTCAE v4.0

PBT was observed in 2 patients. Grade 4 late toxicities occurred in 6 patients (7 %) with 6 events (encephalomyelitis infection 2, optic nerve disorder 4).

Case 1: optic nerve disorder Gr. 4

A 79-year-old man with T4 olfactory neuroblastoma of the nasal cavity received PBT alone. At 42 months after PBT, MRI revealed no evidence of malignancy (Fig. 2). However, he gradually became aware of decreased visual acuity 3 years after treatment, and finally became blind at 51 months after treatment.

Detailed information about patients with grade 4 optic nerve disorder is shown in Table 3.

Case 2: brain necrosis Gr. 1

A 68-year-old man whose disease was T4N0M0 squamous cell carcinoma of the nasal cavity received proton beam therapy with cisplatin. Three months after PBT, MRI revealed no evidence of malignancy, and no toxicity. This finding did not change during long-term follow-up for 24 months at 3-month intervals. However, at 24 months after treatment, an edematous change was found in a frontal lobe, and brain necrosis without symptoms was confirmed

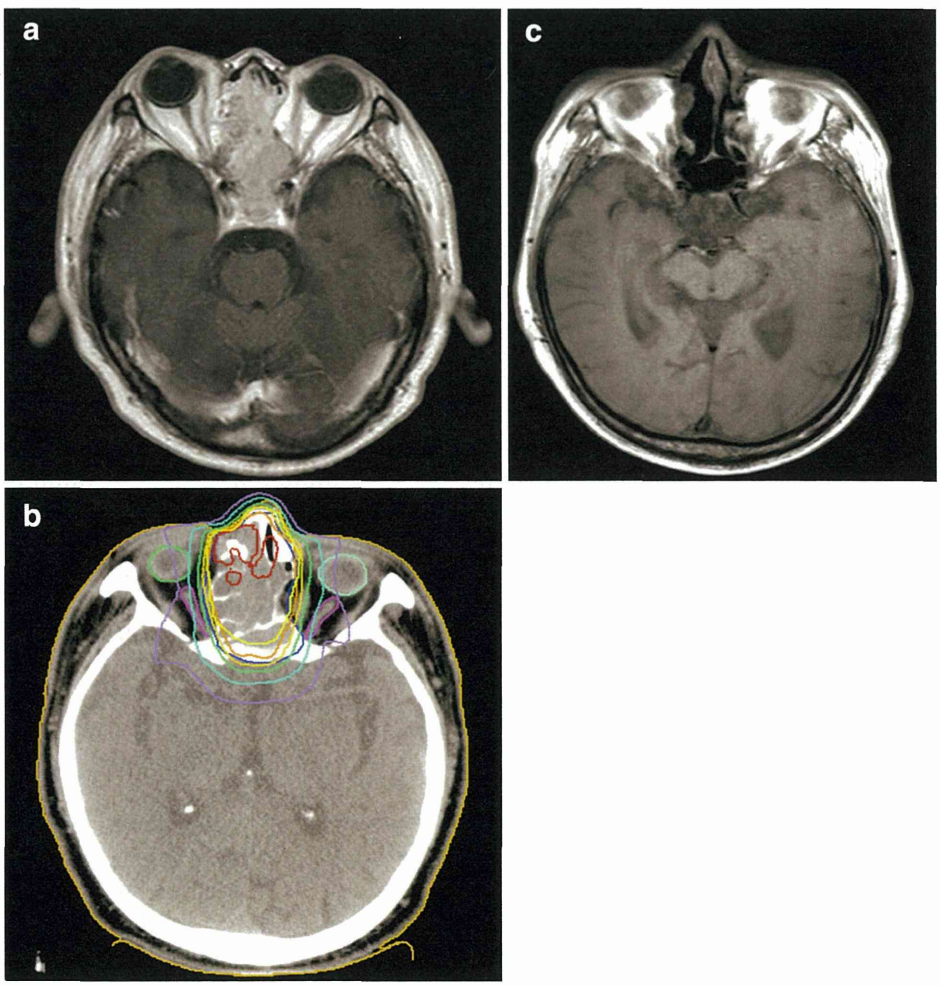

Fig. 2 Optic nerve disorder in a patient treated with proton beam therapy (PBT). **a** Magnetic resonance imaging (MRI) at pretreatment; **b** dose distribution of PBT; **c** MRI at 3 years after treatment. Dose-painting simulation of PBT indicated a maximum dose to the right optic nerve of 61.4 GyE. Although MRI at 3 years after treatment revealed no evidence of malignancy or change in the optic nerve, the patient became blind at 51 months after treatment

Table 3 Grade 4 optic nerve disorder in detail

Gender	Age	Primary site	T stage	Treatment		Chiasm and optic nerve volume >50 Gy/(max)	Time to onset	Status	
M	56	Nasal cavity	1	PBT alone	65 GyE/26 fr	0.5 cc/(63.7 GyE)	6Y2M	Alive w/o disease	8Y2 M
F	52	Nasopharynx	4	PBT alone	65 GyE/26 fr	0.2 cc/(65.3 GyE)	4Y3M	Alive w/o disease	6Y2 M
M	79	Nasal cavity	4	PBT alone	65 GyE/26 fr	0.17 cc/(61.4 GyE)	4Y3M	Alive w/o disease	4Y5 M
M	79	Nasal cavity	4	PBT alone	60 GyE/15 fr	0.03 cc/(53.2 GyE)	1Y5M	Died of disease	4Y6 M

M Male, *F* female, *Y* years, *M* months, *PBT* proton beam therapy, *w/o* without

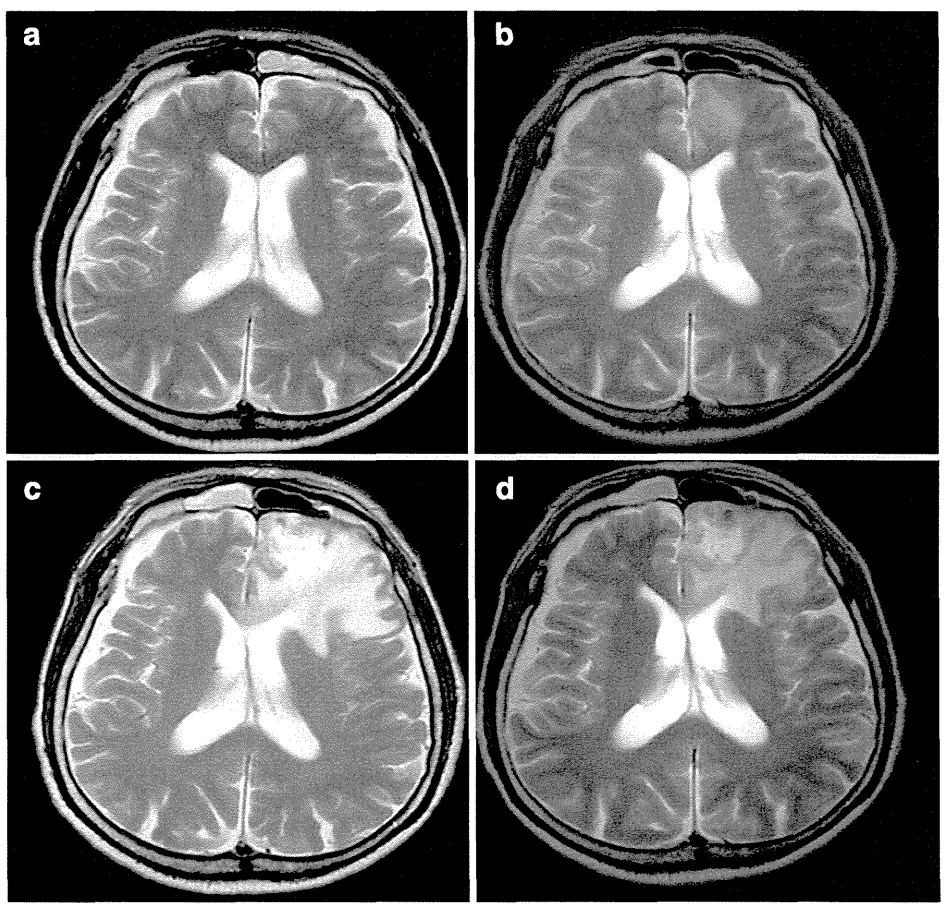

Fig. 3 Brain necrosis in a patient treated with PBT: MRI at pretreatment (**a**), 2 years after treatment (**b**), 2.5 years after treatment (**c**), and 3 years after treatment (**d**). The volume of brain to which was prescribed > 60 GyE was 17.5 cc and maximum dose was 65 GyE. The patient developed no serious symptoms throughout the follow-up period, and he presently remains alive at more than 4 years after treatment

at 30 months after treatment. This late toxicity gradually improved on MRI without additional treatment (Fig. 3).

Univariate analyses

In univariate analysis, T stage (T4 vs. non-T4), sex, age (less than 65 years vs. 65 years or more),induction chemotherapy (on vs. off), concurrent chemotherapy(on vs. off), dose per fraction ($\geq$2.5 Gy vs. <2.5 Gy), and primary site (nasal cavity vs. others) were investigated. However, no significant factors with an impact on the frequency of brain necrosis and optic nerve disorder were identified (Table 4).

Mild to serious optic nerve disorder as late toxicities occurred in seven patients with T4 who had not received induction chemotherapy; these did not occur in patients with T4 who had received induction chemotherapy.

Discussion

This study clarified details of the late toxicity profile of PBT and late toxicity. The several previous reports of late toxicity following radiotherapy for the intracranial region have shown considerable variation in frequency. We

Table 4 Univariate analysis

Total		Brain necrosis			Optic nerve disorder		
		% ≥ Gr. 1	Odds ratio	95 % CI	% ≥ Gr. 2	Odds ratio	95 % CI
T4	54	9.3	1.73	0.32–9.47	14.9	2.53	0.49–13.0
Non-T4	36	5.6			5.6		
Male	52	3.8	0.29	0.60–1.43	11.5	1.46	0.39–5.48
Female	38	13.2			7.9		
65<	66	7.6	0.91	0.19–4.38	10.6	1.36	0.26–7.06
65≥	24	8.3			8.3		
Induction chemotherapy (+)	20	5.0	1.12	0.21–6.03	5.0	0.36	0.04–3.00
(−)	70	8.6			10.0		
Concurrent chemotherapy (+)	11	0.0	–	–	0.0	–	–
(−)	79	8.9			11.4		
≤2.5 Gy/1 fr	76	7.9	1.11	0.14–8.50	9.2	0.64	0.15–2.79
>2.5 Gy/1 fr	14	7.1			14.3		
Nasal cavity	62	6.5	0.60	0.14–2.51	8.1	1.13	0.23–5.47
Others	28	10.7			7.1		
T4	54						
T4 + induction	18	10.5	0.82	0.14–4.99	0.0	–	–
T4 w/o induction	36	11.1			19.4		

consider that a relatively short observation period will result in the underestimation of late toxicity.

Debus et al. [13] reported an incidence of chronic therapy-induced toxicity on median follow-up of 35 months (range, 3 months to 12 years) in 189 patients who underwent fractionated radiotherapy of only 1 % for grades 1–2 toxicity and 2.1 % for grade 3 disease.

With a median follow-up of 56 months, in contrast, Lee et al. [14] reported the unexpected development of severe late complications in 34.6 % of patients receiving hypofractionated stereotactic body radiotherapy (SBRT) as a boost treatment.

In our present data, median time to onset of grade 2 or greater late toxicity except cataract was 39.2 months (range, 2.7–99.8 months). Further, although only 5 patients (5.5 %) had severe late toxicities (≥grade 3) within 3 years after treatment, 17 patients (18.9 %) experienced 20 events during the total follow-up period. Mizoe et al. [15]. reported the late toxicity profile of carbon-ion therapy for their series of head and neck cancer patients of 52 (22 %, 52/236) events of all grades, and four cases of blindness. Previous reports are summarized in Table 5.

With regard to brain necrosis, several investigators [16–18] reported that severe brain injury was usually irreversible, and sometimes fatal. Surgical resection of a focal region of necrosis can be of benefit and may be life saving [19]. On the other hand, little is known about the outcome of mild or intermediate brain injury. In the present study, we found that some cases of mild or intermediate brain necrosis improved spontaneously after a long period.

In our present study, we experienced many events that would not usually be encountered without long-term follow-up, and an adequate understanding of the toxicity profile of PBT in these patients thus requires long-term follow-up. For T4 disease, severe late toxicities might be avoided by induction chemotherapy. We speculate that subsequent decrease in tumor size after PBT might have an positive impact on decrease in irradiation dose to the brain.

As for efficacy, Zenda et al. [10] reported a 5-year overall survival rate with PBT for unresectable carcinoma of the paranasal sinuses of 55.0 %, whereas Hoppe et al. reported a 5-year survival rate of definitive (chemo)radiotherapy for these patients of only 15 %. These results emphasize the ongoing need for considerable improvement in treatment strategies for these conditions.

One major limitation of this study warrants mention. The precision of dose calculations was made uncertain by the internal heterogeneity, which in turn prevented any medical physics analysis of the late toxicity profile. In particular, precise analysis of dosage from the current pencil-beam dosimeter algorithm is not possible [20].

As part of an ongoing physics evaluations, our group is presently conducting further recalculations of treatment plans for patients with fatal late toxicity using Monte Carlo methods.

Table 5 Previous reports of late toxicity

Age (range)					Follow-up period				
Author	Year	Disease	Pt No.	Treatment	Per fraction	Total dose	Median (range)	Late toxicity in detail (%)	
Schulz-Ertner et al.	2005	ACC of skull base	53	24: RT-FSRT/ IMRT boost	–	70 Gy	24 (2–92) M	≥Gr. 3 late toxicity	1.8
				29: RT-CI boost	54 Gy–3 GyEx6	72 GyE	16 (2–60) M		
Uy et al.	2002	Intracranial meningioma	40	25: Ope-IMRT	1.7–2.0 Gy	40–56 Gy	30 (6–71) M	≥Gr. 3 late toxicity	7.5
				15: IMRT					
Debus et al.	2001	Skull base meningioma	189	RT alone	1.8 Gy	56.8 Gy	35 (3–144) M	≥Gr. 3 late toxicity	2.1
Pehlivan et al.	2011	Skull base tumor	62	PBT alone	1.8–2.0 GyE	63–74 GyE	38 (14–92) M	≥Gr. 3 TL toxicity	3.2
								≥Gr. 1 TL toxicity	11.2
Weber et al.	2012	Intracranial meningioma	39	31: Ope-PBT	–	55.5–66.1 GyE	49.3 (11.5–93.3) M	5-year toxicity free survival	84.5
				8: PBT				≥Gr. 3 late toxicity	12.8
Lee et al.	2012	Head and neck cancer	26	EBRT-SBRT	EBRT: 45–50.4 Gy/25–28 fr SBRT: 10–25 Gy/3–5 fr		56 (27.6–80.2) M	≥Gr. 4 late toxicity	3.8
									34.6
								≥Gr. 3 late toxicity	
Mizoe et al.	2012	Head and neck cancer	236	Carbon-ion therapy	3.6 GyE (4GyE)	57.6 GyE (64 GyE)	<60 months	All grade late toxicity	22.0
Present study		Nasal/paranasal malignancies and skull base tumors	90	16: Ope-PBT(+CDDP)	2.0–4.0 GyE	60–70 GyE	59.7 (12.4–169.7) M	≥Gr. 4 late toxicity	6.6
				74: PBT(+CDDP)				≥Gr. 3 late toxicity	21.1

Pt patient, *No* number, *ACC* adenoid cystic carcinoma, *RT* radiotherapy, *FSRT* fractionated stereotactic radiotherapy, *IMRT* intensity modulated radiotherapy, *M* months, *Gr* Grade, *PBT* proton beam therapy, *TL* temporal lobe, *EBRT* external-beam radiotherapy, *SBRT* stereotactic body radiotherapy

In conclusion, the late toxicity profile of proton beam therapy in patients with malignancy involving the nasal cavity, para-nasal sinuses, or skull base was partly clarified. Because late toxicity can occur as late as 5 years after treatment, long-term follow-up is necessary.

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

References

1. Ketcham AS, Wilkins RH, Vanburen JM, Vanburen JM, Smith RR (1963) A combined intracranial facial approach to the paranasal sinuses. Am J Surg 106:698–703
2. Blanco AI, Chao KS, Ozyigit G et al (2004) Carcinoma of paranasal sinuses: long-term outcomes with radiotherapy. Int J Radiat Oncol Biol Phys 59(1):51–58
3. Hoppe BS, Stegman LD, Zelefsky MJ et al (2007) Treatment of nasal cavity and paranasal sinus cancer with modern radiotherapy techniques in the postoperative setting: the MSKCC experience. Int J Radiat Oncol Biol Phys 67(3):691–702
4. Jansen EP, Keus RB, Hilgers FJ, Haas RL, Tan IB, Bartelink H (2000) Does the combination of radiotherapy and debulking surgery favor survival in paranasal sinus carcinoma? Int J Radiat Oncol Biol Phys 48(1):27–35
5. Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T (2001) Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. Cancer (Phila) 92(12):3012–3029
6. Snyers A, Janssens GO, Twickler MB et al (2009) Malignant tumors of the nasal cavity and paranasal sinuses: long-term outcome and morbidity with emphasis on hypothalamic-pituitary deficiency. Int J Radiat Oncol Biol Phys 73(5):1343–1351
7. Dirix P, Nuyts S, Geussens Y et al (2007) Malignancies of the nasal cavity and paranasal sinuses: long-term outcome with conventional or three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 69(4):1042–1050
8. Hoppe BS, Nelson CJ, Gomez DR et al (2008) Unresectable carcinoma of the paranasal sinuses: outcomes and toxicities. Int J Radiat Oncol Biol Phys 72(3):763–769

9. Nutting CM, Morden JP, Harrington KJ et al (2011) Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 12(2):127–136
10. Zenda S, Kohno R, Kawashima M et al (2011) Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses. Int J Radiat Oncol Biol Phys 81(5):1473–1478
11. Nishimura H, Ogino T, Kawashima M et al (2007) Proton-beam therapy for olfactory neuroblastoma. Int J Radiat Oncol Biol Phys 68(3): 758–762
12. Fuji H, Nakasu Y, Ishida Y et al (2011) Feasibility of proton beam therapy for chordoma and chondrosarcoma of the skull base. Skull Base 21(3):201–206
13. Debus J, Wuendrich M, Pirzkall A et al (2001) High efficacy of fractionated stereotactic radiotherapy of large base-of-skull meningiomas: long-term results. J Clin Oncol 19(15):3547–3553
14. Lee DS, Kim YS, Cheon JS et al (2012) Long-term outcome and toxicity of hypofractionated stereotactic body radiotherapy as a boost treatment for head and neck cancer: the importance of boost volume assessment. Radiat Oncol 7:85
15. Mizoe JE, Hasegawa A, Jingu K et al (2012) Results of carbon ion radiotherapy for head and neck cancer. Radiother Oncol 103(1):32–37
16. Stelzer KJ (2000) Acute and long-term complications of therapeutic radiation for skull base tumors. Neurosurg Clin N Am 11(4):597–604
17. Sheline GE, Wara WM, Smith V (1980) Therapeutic irradiation and brain injury. Int J Radiat Oncol Biol Phys 6(9):1215–1228
18. Marks JE, Baglan RJ, Prassad SC, Blank WF (1981) Cerebral radionecrosis: incidence and risk in relation to dose, time, fractionation and volume. Int J Radiat Oncol Biol Phys 7(2):243–252
19. Woo E, Lam K, Yu YL, Lee PW, Huang CY (1987) Cerebral radionecrosis: is surgery necessary? J Neurol Neurosurg Psychiatry 50(11):1407–1414
20. Hotta K, Kohno R, Takada Y et al (2010) Improved dose-calculation accuracy in proton treatment planning using a simplified Monte Carlo method verified with three-dimensional measurements in an anthropomorphic phantom. Phys Med Biol 55(12):3545–3556

Journal of Radiation Research, 2014, 55, 568–574
doi: 10.1093/jrr/rrt143 Advance Access Publication 20 January 2014

Evaluating positional accuracy using megavoltage cone-beam computed tomography for IMRT with head-and-neck cancer

Kana MOTEGI*, Ryosuke KOHNO, Takashi UEDA, Toshiyuki SHIBUYA, Takaki ARIJI, Mitsuhiko KAWASHIMA and Tetsuo AKIMOTO

National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan
*Corresponding author. Tel: +81-4-7133-1111; FAX: +81-4-7134-7048; Email: kmatsub@east.ncc.go.jp

(Received 4 June 2013; revised 17 November 2013; accepted 18 November 2013)

Accurate dose delivery is essential for the success of intensity-modulated radiation therapy (IMRT) for patients with head-and-neck (HN) cancer. Reproducibility of IMRT dose delivery to HN regions can be critically influenced by treatment-related changes in body contours. Moreover, some set-up margins may not be adaptable to positional uncertainties of HN structures at every treatment. To obtain evidence for appropriate set-up margins in various head and neck areas, we prospectively evaluated positional deviation (δ values) of four bony landmarks (i.e. the clivus and occipital protuberance for the head region, and the mental protuberance and C5 for the neck region) using megavoltage cone-beam computed tomography during a treatment course. Over 800 δ values were analyzed in each translational direction. Positional uncertainties for HN cancer patients undergoing IMRT were evaluated relative to the body mass index. Low positional accuracy was observed for the neck region compared with the head region. For the head region, most of the δ was distributed within ±5 mm, and use of the current set-up margin was appropriate. However, the δ values for the neck region were within ±8 mm. Especially for overweight patients, a few millimeters needed to be added to give an adequate set-up margin. For accurate dose delivery to targets and to avoid excess exposure to normal tissues, we recommend that the positional verification process be performed before every treatment.

Keywords: positional accuracy; body mass index; head and neck; IMRT; MV-CBCT

INTRODUCTION

Accurate dose delivery is essential for the success of intensity-modulated radiation therapy (IMRT) in patients with head-and-neck (HN) cancer, due to the steep dose gradient between the planning target volume (PTV) and the adjacent organs at risk (e.g. spinal cord and parotid glands). Reproducibility of the patient's position during IMRT is critically important. In general, the patient is immobilized with a customized thermoplastic mask and pillows. The body is positioned on a couch by matching external marks on the mask to the isocenter indicated by lasers. Skin marks on the patient's shoulders and chest are used to assist set-up.

Researchers have used various imaging procedures [1], such as orthogonal mega- or kilovoltage (kV) X-ray radiographic imaging [2–4], computed tomography (CT) on rails [5], and 3D cone-beam computed tomography (CBCT) [4, 6, 7], to verify patient positioning during set-up for IMRT. A recent study evaluated the positional accuracy of HN cancer patients using 3D imaging procedures, revealing positional deviations of 3 mm and ≥5 mm in 18.7 and 4.1% of set-ups, respectively, with kV-CBCT, compared with 11.2 and 1.7%, respectively, with 2D kV radiographic imaging [4]. Differences between the procedures were mainly attributed to the relative flexibility and possible rotation of the HN structures. Complex patterns of set-up errors resulting from these complications were also observed when CT on rails, which found a difference of 2–6 mm for the distance between two bony landmarks at the second or sixth cervical vertebra and the palatine process of the maxillary bone [1]. Various magnitudes of set-up errors among multiple regions-of-interest, which were frequently larger than those detected at the isocenter, were observed using kV-CBCT [7]. When 3D imaging procedures were used, geometrical uncertainties caused by the rotation/flexibility of HN structures became apparent. These findings imply that a variety of set-up margins are required for the different portions of the head and neck during IMRT planning.

Reproducibility of HN IMRT delivery could be critically influenced by changes in body contours derived from e.g. malnutrition or loss of postsurgical edema during treatment [8, 9]. In addition to loose fitting of immobilization masks and pillows, such changes may cause unexpected over- or under-IMRT dosing to targets and critical organs, which should be corrected with replanning of IMRT [10–12]. Set-up margins applied for the clinical target volume (CTV) and the risk organs are decided on the basis of clinical experiences and reported values. Thus, these margins may not be adaptable to the geometrical uncertainties of patient positioning during IMRT, such as the rotation/flexibility of HN structures and changes in body contours.

To obtain evidence for appropriate set-up margins for various HN portions, using 3D megavoltage (MV)-CBCT, we prospectively evaluated the positional deviation for four bony landmarks (clivus, occipital protuberance, mental protuberance, and C5) during a course of HN IMRT. Additionally, because obese patients generally have difficulty maintaining their weight during treatment and tend to have low positional reproducibility, positional uncertainties were evaluated relative to the body mass index (BMI).

MATERIALS AND METHODS

Patient characteristics and set-up

A total of 67 patients with HN cancer who underwent IMRT were included in this study. The study was approved by our institution's protocol review board, and patients gave their written consent prior to their participation. Characteristics for the patients are listed in Table 1. As defined by the World Health Organization, patients with BMI < 18, 18 ≤ BMI < 25, and 25 ≤ BMI were classified as underweight, normal weight and overweight, respectively. For set-up, all patients were immobilized in a supine position, with thermoplastic fixation masks and customized vacuum pillows extended to the shoulders from the back of the head (Fig. 1). Fixation devices were attached to the treatment couch by an index bar.

Table 1. Patient characteristics

Characteristics	
Sex (*n*)	
Male	51
Female	16
Total	67
Age (y)	
Median (Min.–Max.)	59 (18–82)
BMI classification (*n*)	
Underweight (BMI < 18)	10
Normal weight (18 ≤ BMI < 25)	37
Overweight (25 ≤ BMI)	12
Unknown	8
Irradiated site (*n*)	
Nasopharynx	13
Oropharynx	15
Hypopharynx	7
Parotid	3
Paranasal sinus	6
Oral cavity	15
Neck	6
Unknown	2

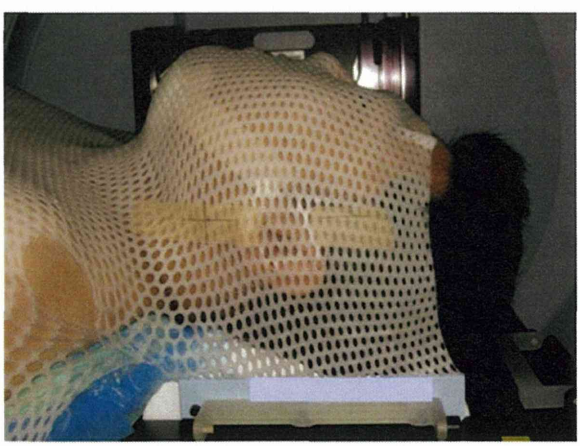

Fig. 1. Patient immobilization for HN IMRT.

Volume acquisition

Once patients were positioned on a treatment couch using their personal masks and vacuum pillows, they were scanned by MV-CBCT mounted on an Oncor linear accelerator (Siemens Medical Solutions, Concord, CA). An amorphous-silicon flat panel detector with an active detector area of 41 cm × 41 cm and a spatial resolution of 1024 × 1024 pixels was used for volumetric acquisition of the MV-CBCT. The voxel size of the reconstructed images was 1.07 mm × 1.07 mm × 1 mm. The maximum field of view (FOV) was 27.4 cm × 27.4 cm at a source-to-axis distance of 100 cm. CT images were reconstructed using 200 projections during 200° of gantry rotation. The CBCT image reconstruction process has been described elsewhere [13–15]. Geometrical distortion of the reconstructed images was evaluated using a phantom with 1-cm square grids. Exposure corresponded to 2.1 cGy at a depth of 10 cm in solid water slabs measured with an ionization chamber.

To avoid clinical overloading and excess exposure to patients, volume acquisition was scheduled as follows: continuously during the first 5 d to confirm reproducibility of the isocenter marking on the masks, and once every 5 d

thereafter. When a set-up error ≥3mm was detected, another volume acquisition was performed the next day.

Verification of patient position

Figure 2 shows the four bony landmarks used for the verification of patient position. The clivus was used for positional verification in the skull because, in many cases, a steep dose gradient is observed at this site to spare the brain stem. The occipital/mental protuberances and C5 were selected to evaluate deviation due to HN flexibility/rotation. For each landmark, discrepancy of the position between treatment and treatment planning (δ) was measured by manual registration between MV-CBCT and simulation-CT (Toshiba Medical Systems, Tokyo, Japan) using MVision software (Siemens Medical Solutions, Concord, CA). Simulation-CT had a voxel size of 1 mm × 1 mm × 1 mm. Since the edge of bony structures was detected simply in the CT images compared with the center of bony structures, the edge of bony structures was used in the manual registration. To improve reproducibility of the positional verification, the manual registration was performed changing the contrast of the CT images variously and widely, and prevented the edge of bony structures from being missing on CT images. Therapists were trained in the manual to reduce variations between individuals.

Statistical analysis

For each landmark, > 800 δ values were analyzed in the three translational directions of left–right (LR), craniocaudal (CC), and anteroposterior (AP). The mean and range (minimum to maximum) of δ values were obtained. To evaluate positional accuracy for HN IMRT, 1σ of δ values were calculated. The statistical analysis was performed for all patients, and patients were categorized by BMI.

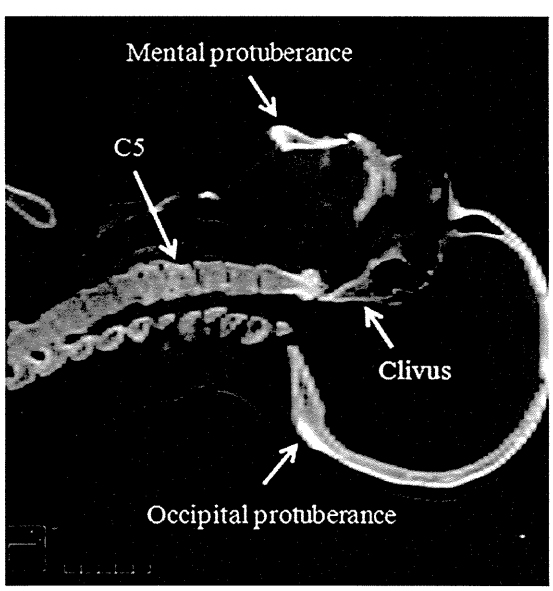

Fig. 2. Verification of patient position in HN IMRT. Positional reproducibility was evaluated with four body landmarks: the clivus, the occipital protuberance, the mental protuberance, and C5.

RESULTS

Table 2 shows statistics of the δ values for each landmark. Overall, patients tended to shift to the left, caudal and dorsal side within 2 mm. The 1σ values for the clivus and occipital protuberance (range, 1.2–1.7 mm) were less than those for the mental protuberance and C5 (range, 1.5–2.3 mm). Thus, the neck region (mental protuberance and C5) had lower positional accuracy than the head region (clivus and occipital protuberance). The mental protuberance had maximum δ and 1σ of 1 cm and 2.8 mm, respectively, which were found in overweight patients.

To evaluate differences in positional accuracy by BMI, δ values were plotted with the frequency distributions (Fig. 3). The positive side of the horizontal axis in Fig. 3 represents the right, caudal and dorsal side of the patients, and the vertical axis represents frequencies. For the clivus (a), occipital protuberance (b), mental protuberance (c), and C5 (d), the δ values were distributed in a near-normal distribution. Generally, most of the δ values for the clivus and occipital protuberance were distributed within ±5 mm, whereas those for the mental protuberance and C5 were distributed within ±8 mm. Compared with normal weight patients, overweight patients had a wider and more even distribution of δ values in the mental protuberance and C5. In underweight patients, the mental protuberance was shifted to the right side, whereas it was left-shifted for normal weight and overweight patients. To evaluate equality of the positional accuracy among the patient groups, an F-test was performed on the δ values classified by the patient's BMI. The significance level was determined to <0.02 by using a Bonferroni correction for the multiple comparison. In the neck region, (including mental protuberance and C5), the variances of δ values were more significantly different among the patient groups than in the head region (including the clivus and the occipital protuberance). Therefore, it was implied that the positional accuracy for the neck region, including the mental protuberance and C5, tended to be affected by the patient's BMI.

In the time trend of δ values, patients tended to shift slightly to the right and foot side during a course of treatment. A maximum shift of 0.8 mm to the foot direction was observed for the mental protuberance. No shift along the AP direction was observed in any landmark. Patients maintained constant positional accuracy during a course of treatment.

DISCUSSION

In this study, lower positional reproducibility was found in the neck region compared with the head region of HN cancer patients, and the patient's BMI affected the positional

Table 2. Statistical analysis of δ[a]

		Clivus			Occipital protuberance			Mental protuberance			C5		
		LR	**CC**	**AP**	**LR**	**CC**	**AP**	**LR**	**CC**	**AP**	**LR**	**CC**	**AP**
All patients	Number of δ values	867	858	858	824	824	824	813	813	813	831	831	831
	Median (mm)	−1	1	0	−1	0	1	0	1	0	0	1	2
	(Range)	(−4 to 3)	(−4 to 6)	(−3 to 4)	(−6 to 3)	(−7 to 6)	(−4 to 5)	(−4 to 5)	(−7 to 8)	(−8 to 10)	(−8 to 6)	(−6 to 6)	(−7 to 9)
	1σ (mm)	1.2	1.4	1.2	1.4	1.7	1.3	1.5	2.3	1.9	1.9	1.7	2.3
Underweight	Number of δ values	123	123	123	123	123	123	112	112	112	112	112	112
	Median (mm)	−1	1	1	−1	1	1	1	1	0	0	1	2
	(Range)	(−3 to 2)	(−3 to 6)	(−1 to 4)	(−5 to 3)	(−4 to 6)	(−2 to 4)	(−3 to 4)	(−2 to 4)	(−2 to 4)	(−5 to 5)	(−2 to 5)	(−2 to 7)
	1σ (mm)	1.3	1.5	0.9	1.4	1.6	1.1	1.6	1.5	1.2	1.7	1.5	1.8
Normal-weight	Number of δ values	512	512	512	501	501	501	501	501	501	501	501	501
	Median (mm)	−1	1	0	−1	0	1	0	2	0	0	1	1
	(Range)	(−4 to 2)	(−4 to 5)	(−3 to 4)	(−6 to 3)	(−5 to 5)	(−4 to 5)	(−4 to 5)	(−6 to 7)	(−8 to 6)	(−7 to 4)	(−4 to 6)	(−4 to 8)
	1σ (mm)	1.1	1.4	1.2	1.3	1.7	1.3	1.5	2.2	1.7	1.6	1.7	2.2
Overweight	Number of δ values	158	158	158	147	147	147	158	158	158	158	158	158
	Median (mm)	0	0	1	−1	−1	1	1	1	0	−1	0	2
	(Range)	(−4 to 2)	(−4 to 5)	(−3 to 4)	(−4 to 2)	(−7 to 4)	(−3 to 4)	(−4 to 4)	(−7 to 8)	(−4 to 10)	(−8 to 6)	(−6 to 3)	(−4 to 9)
	1σ (mm)	1.2	1.5	1.2	1.4	1.9	1.2	1.5	2.8	2.6	2.3	1.8	2.1

Translational directions are expressed in left–right (LR), craniocaudal (CC), and anteroposterior (AP) directions. [a]Discrepancy of the position between treatment and treatment planning.

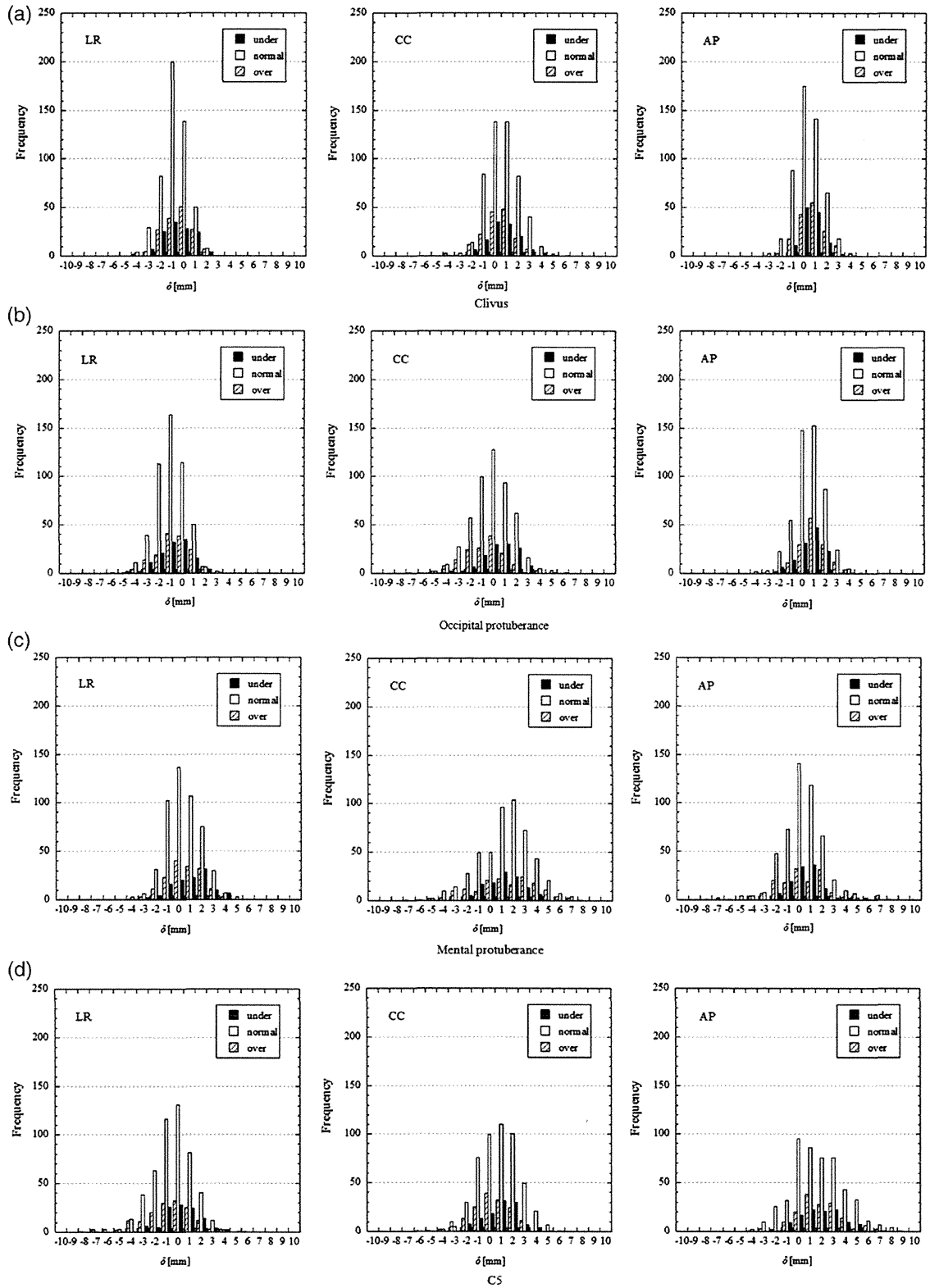

Fig. 3. Frequency distribution of positional deviation for four bony landmarks: (**a**) the clivus, (**b**) the occipital protuberance, (**c**) the mental protuberance, and (**d**) C5. Positional reproducibility was evaluated in three translational directions of left–right (LR), craniocaudal (CC) and anteroposterior (AP). Moreover, patients were classified into underweight (under), normal weight (normal), and overweight (over).

Table 3. Evaluation of the current set-up margin for HN IMRT

	Number of $\|\delta^a\|$ >5 mm (%[b])											
	Clivus			Occipital protuberance			Mental protuberance			C5		
	LR	CC	AP	LR	CC	AP	LR	CC	AP	LR	CC	AP
All patients	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	23 (2.8)	14 (1.7)	12 (1.4)	2 (0.2)	43 (5.2)
Underweight	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)
Normal weight	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	13 (2.6)	5 (1.0)	1 (0.2)	1 (0.2)	22 (4.4)
Overweight	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	10 (6.3)	9 (5.7)	8 (5.1)	1 (0.6)	10 (6.3)

[a]Discrepancy of the position between treatment and treatment planning. [b]Percentage of $|\delta|$ >5 mm in patient groups.

accuracy of HN IMRT. Overweight patients generally lose fat easily from under the lower jaw, the back of the neck, and the shoulders. The resulting looseness of the fixation mask markedly reduced the reproducibility of patient positioning. It will be very interesting to evaluate the relation between patients' surfaces and positional accuracy among the patient groups using volume data such as CBCT. In addition, it is potentially difficult to make fixation masks that will adjust to rapid differences in shape between the lower neck and upper chest.

In treatment planning for HN IMRT, a set-up margin of 5 mm was applied to any portion of the HN region. Most of the δ values for the clivus and occipital protuberance were distributed within ±5 mm. Thus, the current set-up margin for the head region was reasonably adequate. On the other hand, most of the δ values for the mental protuberance and C5 were within ±8 mm, suggesting that the set-up margin for the neck region should be expanded by a few millimeters. Furthermore, the frequency of $|\delta| > 5$ mm was evaluated (Table 3). In particular, the percentage of $|\delta| > 5$ mm out of the number of δ values for overweight patients was > 5% in the CC and AP directions for the mental protuberance, and the LR and AP directions for C5.

It was reported that the positional deviation of patients decreased the dose delivered to the PTV by 3–14% and caused excess exposure to critical organs [4]. Thus, positional verification before beam delivery is essential for successful HN IMRT. However, many facilities schedule specific days for the positional verification and do not perform such verification at every treatment. Therefore, we strongly suggest that the positional verification process be repeated frequently, preferably before every treatment, to prevent excess radiation exposure to adjacent critical organs by expansion of the PTV. In this context, the use of recent low-exposure 3D imaging devices in image-guided radiation therapy may be very useful.

CONCLUSION

Deviation of the patient position during a course of treatment was evaluated in HN IMRT. The positional deviation was locally different in the HN regions, with lower positional reproducibility being observed in the neck. Overweight patients had the lowest positional accuracies. An increase in the set-up margin of a few millimeters was required if the CTV and critical organs were located in the neck region. For accurate dose delivery to targets and to spare normal tissues, we recommend repeating the positional verification process often and using image-guided radiation therapy.

REFERENCES

1. van Herk M. Different styles of image-guided radiotherapy. *Semin Radiat Oncol* 2007;**17**:258–67.
2. Hurkmans C-W, Remeijer P, Lebesque J-V *et al.* Set-up verification using portal imaging; review of current clinical practice. *Radiother Oncol* 2001;**158**:105–20.
3. Lawson J-D, Elder E, Fox T *et al.* Quantification of dosimetric impact of implementation of on-board imaging (OBI) for IMRT treatment of head-and-neck malignancies. *Med Dosim* 2007;**32**:287–94.
4. Li H, Zhu X-R, Zhang L *et al.* Comparison of 2D radiographic images and 3D cone beam computed tomography for positioning head-and-neck radiotherapy patients. *Int J Radiat Oncol Biol Phys* 2008;**71**:916–25.
5. Zhang L, Garden A-S, Lo J *et al.* Multiple regions-of-interest analysis of setup uncertainties for head-and-neck cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;**64**:1559–69.
6. Gayou O, Parda D-S, Johnson M *et al.* Patient dose and image quality from mega-voltage cone beam computed tomography imaging. *Med Phys* 2007;**34**:499–506.
7. van Kranen S, van Beek S, Rasch C *et al.* Setup uncertainties of anatomical sub-regions in head-and-neck cancer patients after offline CBCT guidance. *Int J Radiat Oncol Biol Phys* 2009;**73**:1566–73.
8. Donaldson S-S, Lenon R-A. Alterations of nutritional status: impact of chemotherapy and radiation therapy. *Cancer* 1979;**43**:2036–52.
9. Chencharick J-D, Mossman K-L. Nutritional consequences of the radiotherapy of head and neck cancer. *Cancer* 1983;**51**:811–5.
10. Barker J-L, Jr, Garden A-S, Ang K-K *et al.* Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an

integrated CT/linear accelerator system. *Int J Radiat Oncol Biol Phys* 2004;**59**:960–70.
11. Hong T-S, Tome W-A, Chappell R-J *et al.* The impact of daily setup variations on head-and-neck intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2005;**61**:779–88.
12. Hansen E-K, Bucci M-K, Quivey J-M *et al.* Repeat CT imaging and replanning during the course of IMRT for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2006;**64**: 355–62.
13. Pouliot J, Bani-Hashemi A, Chen J *et al.* Low-dose megavoltage cone-beam CT for radiation therapy. *Int J Radiat Oncol Biol Phys* 2005;**61**:552–60.
14. Morin O, Gillis A, Chen J *et al.* Megavoltage cone-beam CT: System description and clinical applications. *Med Dosim* 2006;**31**:51–61.
15. Gayou O, Miften M. Commissioning and clinical implementation of a mega- voltage cone beam CT system for treatment localization. *Med Phys* 2007;**34**:3183–92.

Accelerated radiotherapy for T1 to T2 glottic cancer

Atsushi Motegi, MD, PhD,[1*] Mitsuhiko Kawashima, MD, PhD,[1] Satoko Arahira, MD,[1] Sadamoto Zenda, MD,[1] Masamichi Toshima, MD,[1] Masakatsu Onozawa, MD,[1] Ryuichi Hayashi, MD,[2] Tetsuo Akimoto, MD, PhD[1]

[1]Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, [2]Division of Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, Chiba, Japan.

Accepted 19 February 2014
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.23641

ABSTRACT: *Background.* Accelerated fractionation radiotherapy (RT) was administered in an attempt to improve the local control rates in patients with T1/T2 N0 glottic cancer.

Methods. Medical charts of 148 consecutive patients who had undergone RT using 2.4 Gray (Gy) once-daily fractionation between July 1999 and April 2007 were reviewed.

Results. Of 104 patients with T1 disease treated by RT, 82 received 60 Gy/25 fractions, and the remaining 22 with large tumor volumes and/or slow response to RT received 64.8 Gy/27 fractions. All 44 patients with T2 disease received 64.8 Gy/27 fractions. The 5-year local control and overall survival (OS) rates were 93% and 96%, respectively, in patients with T1 disease, and 77% and 91%, respectively, in patients with T2 disease. No severe acute toxicities were observed, although 2 patients (1%) developed severe late toxicity.

Conclusion. Accelerated RT for early glottic cancer is feasible, with encouraging local control rates. © 2014 Wiley Periodicals, Inc. *Head Neck* 00: 000–000, 2014

KEY WORDS: early glottic cancer, accelerated fractionation radiotherapy, local control, laryngeal preservation, adverse events

INTRODUCTION

Early glottic cancer (T1–2, N0M0) has been treated definitively by conventional radiotherapy (RT), with the reported local control rates ranging from 68% to 81%.[1–8] Accumulating evidence shows that RT using an altered fractionation protocol can improve the therapeutic ratio as compared to conventional fractionation RT in patients with squamous cell carcinoma of the head and neck.[9,10] RT regimens using a total dose of approximately 60 Gray (Gy) administered at 2.25 to 2.5 Gy per fraction for T1 and a total dose of approximately 64.8 Gy administered at the same fractional dose for T2 glottic cancer have been evaluated, and better local control rates with acceptable morbidities have been reported.[1,2,4,8,11,12] We started a phase II study in 1999 of an accelerated fractionation protocol for RT: a total dose of 60 Gy administered at 2.4 Gy per fraction × 5 fractions per week for patients with T1 disease, and a total dose of 64.8 Gy administered using the same fractionation protocol for patients with T2 glottic cancer.[13] A total of 47 patients, including 13 with T2 disease, were enrolled from 2 participating centers. The primary endpoints of this study were the frequency and severity of adverse events, and the secondary endpoint was the local control rate. Owing to the lack of availability of cobalt and 4 MV X-rays, 6 MV X-rays were used in the 2 participating institutions. No moderate/severe acute/late adverse events were observed, and the local control rate at 3 years was 92%. Because of the unexpectedly high incidence of normal appearance of the larynx more than a year after the RT, and the relatively high local control rate as compared to our results of RT administered by the conventional fractionation schedule (total RT dose of 60–70 Gy at 2.0 Gy per fraction × 5 fractions per week) in this study, we continued to use this strategy for patients with T1 and T2 glottic cancer. The purpose of this retrospective analysis was to evaluate the long-term results of accelerated fractionation RT for early glottic cancer to confirm its safety and efficacy.

*Corresponding author: A. Motegi, Division of Radiation Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277–8577, Japan. E-mail: amotegi@east.ncc.go.jp

MATERIALS AND METHODS

Patients

Between July 1999 and April 2007, 161 consecutive patients with T1 or T2 glottic cancer underwent definitive RT using an accelerated fractionation protocol at our institution. Of these patients, 23 were participants of the phase II study described above. The study protocol was approved by the institutional ethics committee, and written informed consent for participation in the study was obtained from each of the patients. After the end of patient accrual in October 2001, all patients received RT at 2.4 Gy/fraction once daily; all patients provided written informed consent after receiving thorough information about the expected risks and benefits of this treatment. Staging was performed according to the fifth edition of the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumors (1997). Accordingly,

T1 was defined as a tumor confined to the true vocal cords (T1a: tumor confined to the vocal cord of 1 side; and T1b: tumor involving the vocal cords bilaterally) and T2 was defined as a tumor invading the supraglottis and/or subglottis, without cord fixation. Pretreatment examinations included fiber-optic pharyngolaryngoscopy, physical examination with neck palpation, chest radiography, and gastroesophageal endoscopy. A CT scan of the head and neck with contrast enhancement was not routinely performed during the study period. All patients had biopsy proven squamous cell carcinoma. Thirteen patients were lost to follow-up within 2 years, without evidence of tumor recurrence, and were excluded from the analysis. The remaining 148 patients who could be followed up for more than 2 years from the start of the RT were included in this study.

TABLE 1. Patient characteristics.

Characteristic	No. of patients (%)
Sex	
Male/female	139/9 (94/6)
T classification	
T1a	78 (53)
T1b	26 (17)
T2	44 (30)
Histological differentiation	
W/D	49 (33)
M/D	55 (37)
P/D	6 (4)
NOS	38 (26)

Abbreviations: W/D: well differentiated, M/D: moderately differentiated, P/D: poorly differentiated, NOS: not otherwise specified.

Radiotherapy

All patients underwent CT simulation using thermoplastic masks after being immobilized in the supine position. The imaging was carried out at a slice thickness of 1 to 3 mm, without contrast enhancement. RT was administered using 6 MV X-rays. Opposed lateral fields were used with a 5-mm water equivalent bolus on the surface of the neck to compensate for the X-ray build up. Patients received irradiation once daily, 5 times a week, except on public holidays (unless required to achieve a minimum of 8 fractions within 2 consecutive weeks). The radiation portal was designed to encompass the entire laryngeal box, ranging from 5 cm × 5 cm to 6 cm × 6 cm in size. RT plans were established using the Xio software (Elekta, Stockholm, Sweden). The RT doses were prescribed at arbitrarily defined reference points to ensure complete coverage of the vocal cords within a 95% isodose of the prescribed dose. Every effort was made not to include the entire arytenoid cartilage within the 95% isodose volume; therefore, wedge filters were not routinely used. The prescribed RT dose was 60 Gy administered in 25 fractions for T1 disease and 64.8 Gy administered in 27 fractions for T2 disease. However, the total RT dose was increased to 64.8 Gy for even T1 disease when the tumors had not yet resolved completely after a total dose of 40.8 Gy, or the tumors were bulky, as judged by a single physician (M. K.).

Outcome measures and statistical considerations

The local control rate, laryngeal preservation rate, overall survival (OS) rate, and adverse events were analyzed. Follow-up visits were requested every month for the first 2 years after completion of the RT, at least once every 3 months during the third year, and once every 6 months thereafter. Each follow-up visit included a physical examination and a fiber-optic laryngoscopy. A chest X-ray was obtained at least once within the first 12 months after treatment. Time-to-event analyses from the start of RT were performed using the Kaplan–Meier method. Biopsy-proven recurrence of the primary tumor and total laryngectomy were used as the defining events for calculating the local control rate and laryngeal preservation rate, respectively, and patients who died without these events were censored at the time of the last follow-up examination. Death from any cause was used as the defining event to calculate the OS. The significance of any differences were estimated using the log-rank test. Differences were considered to be significant when the 2-sided p value was $< .05$. Adverse events were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. In addition, we also calculated the cumulative rate of incidence of cerebral infarction to assess the influence of accelerated RT on the risk of cerebrovascular events.

Statistical analysis

All the statistical analyses were performed using the JMP software, version 10.0 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

The patient characteristics are summarized in Table 1. There were 139 male (94%) and 9 female (6%) patients, with a median age of 67 years (range, 46–96 years); 78 patients (53%) had T1a, 26 (17%) had T1b, and 44 (30%) had T2 disease. None of the patients had lymph node or distant metastasis at the time of the initial presentation. The histological differentiation grades of the tumors are shown in Table 1.

Radiotherapy

RT was completed in every patient. Of the 104 patients with T1 disease, 22 (21%) required a total RT dose of 64.8 Gy. The reason for the increase of the total dose in patients with T1 disease was slow response of the tumors to RT in 18 patients and presence of bulky tumors in the remaining 4 patients. All 44 patients with T2 disease received a total radiation dose of 64.8 Gy. The maximum RT dose within the irradiated volume was <107% of the prescribed dose in all patients. The overall treatment time was 36 to 42 days (median, 37 days) in the patients treated at a total dose of 60 Gy, and 38 to 47 days (median, 41 days) in patients treated at a total dose of 64.8 Gy. The overall treatment time was not prolonged by more than 7 days because of acute morbidity in any of the patients.

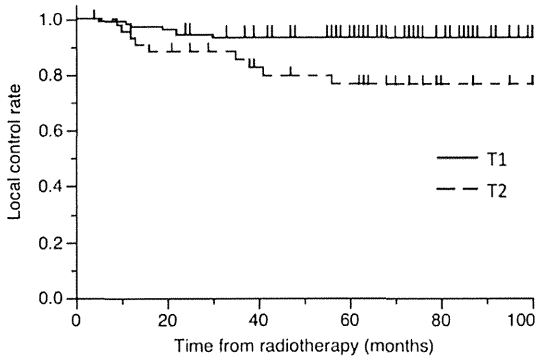

FIGURE 1. Kaplan–Meier estimates of the local control rate in patients with T1 and T2 disease. Solid and dashed lines represent patients with T1 and T2 disease, respectively.

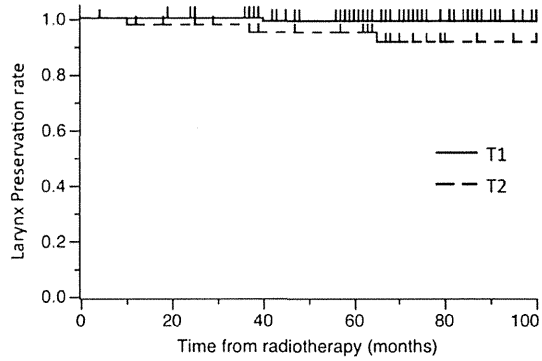

FIGURE 3. Kaplan–Meier estimates of the laryngeal preservation rate. Solid and dashed lines represent patients with T1 and T2 disease, respectively.

Acute toxicity

Grade 2 dermatitis with moist desquamation was observed in almost every patient, but the dermatitis subsided within 2 to 3 weeks in all patients. Severe acute toxicity (grade 3 or more), including pain, mucositis, dermatitis, dysphagia, dyspnea, and voice change, was not observed in any of the patients.

Patterns of failure

The surviving patients were followed up for a median period of 74 months (range, 24–150 months). In total, 19 recurrences were observed: 6 in patients with T1a, 2 in patients with T1b, and 11 in patients with T2 disease. The first site of recurrence was not a distant metastasis in any of the patients. Sixteen of the 19 recurrences were local failure, and all of the 8 recurrences in patients with T1 disease were local. Of the 11 recurrences in patients with T2 disease, 8 occurred at a local station only, 2 at a nodal station without local recurrence, and 1 at both local and nodal stations. The median time to disease recurrence was 17 months (range, 5–110 months). Partial and total laryngectomies were performed as salvage therapy for 12 patients (6 with T1 tumors and 6 with T2 tumors) and 4 patients (1 with a T1 tumor and 3 with T2 tumors), respectively. Two of these patients underwent simultaneous lymph node dissections. The other 2 patients with T2 disease who underwent salvage total laryngectomy showed disease progression and died subsequently. Three patients did not receive salvage therapy and received best supportive care.

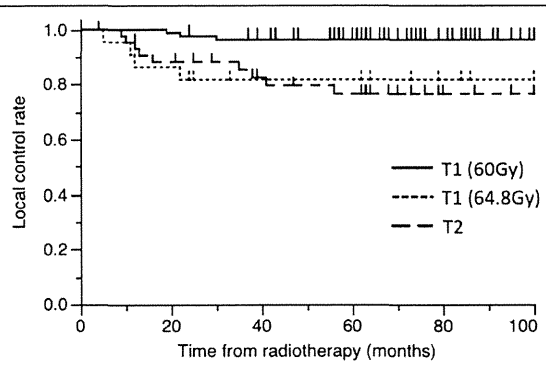

FIGURE 2. Kaplan–Meier estimates of the local control rate in patients with T1 disease treated with 60 Gray (Gy; solid line) or 64.8 Gy (dotted line), and in patients with T2 disease (dashed line).

Local control, laryngeal preservation, and overall survival rates

The local control rates at 3 and 5 years were both 93% (95% confidence interval [CI], 88% to 98%) in patients with T1 tumors and 85% (95% CI, 75% to 96%) and 77% (95% CI, 63% to 90%), respectively, in patients with T2 tumors ($p = .013$). In patients with T1 disease, the local control rate at 5 years was 96% (95% CI, 92% to 100%) in those who received 60 Gy over 25 fractions ($n = 82$), however, whereas the local control rate was 82% (95% CI, 66% to 98%) in patients treated with 64.8 Gy over 27 fractions ($n = 22$; $p = .001$). The local control rate in the 18 patients with slowly responding T1 disease treated with 64.8 Gy was 78% (95% CI, 59% to 97%) at 5 years, and none of the 4 patients with bulky disease treated with 64.8 Gy experienced local recurrence for more than 5 years. The larynx-preservation rates at 3 and 5 years were 100% and 99% (95% CI, 93% to 99%), respectively, in the patients with T1 tumors, and 98% (95% CI, 86% to 99%) and 95% (95% CI, 82% to 99%), respectively, in the patients with T2 tumors ($p = .055$). Of the T1 patients, the larynx-preservation rates at 3 and 5 years were both 100% in the patients with T1 tumors treated with 60 Gy, and 100% and 95% (95% CI, 76% to 99%), respectively, in those treated with 64.8 Gy. The OS rates at 3 and 5 years were 99% (95% CI, 93% to 99%) and 96% (95% CI, 89% to 98%), respectively, in patients with T1 tumors, with both being 91% (95% CI, 77% to 96%) in patients with T2 tumors ($p = .444$). Among the T1 patients, the OS rates at 3 and 5 years were 100% and 97% (95% CI, 89% to 99%), respectively, in the patients with T1 tumors treated with 60 Gy, and 95% (95% CI, 74% to 99%) and 91% (95% CI, 69% to 98%),

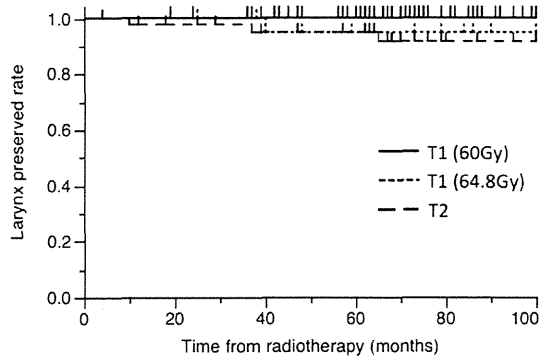

FIGURE 4. Kaplan–Meier estimates of the laryngeal preservation rate in patients with T1 disease treated with 60 Gray (Gy) (solid line) or 64.8 Gy (dotted line), and patients with T2 disease (dashed line).

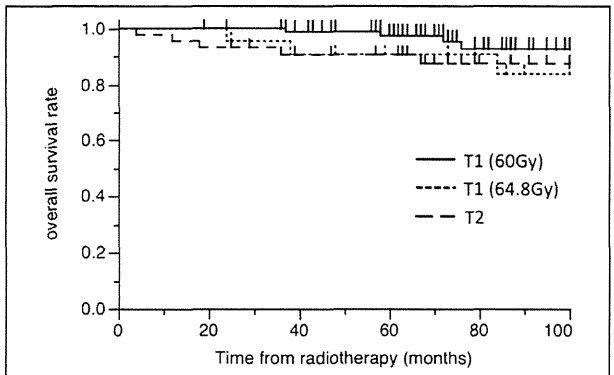

FIGURE 6. Kaplan–Meier estimates of the overall survival in patients with T1 disease treated with 60 Gray (Gy; solid line) or 64.8 Gy (dotted line), and patients with T2 disease (dashed line).

respectively, in the patients with T1 tumors treated with 64.8 Gy. The Kaplan–Meier estimations of the local control rate, larynx-preservation rate, and OS rates are shown in Figures 1, 2, 3, 4, 5, and 6.

Late toxicity

Severe late toxicity occurred in 2 patients (1%). Both of these patients had T2 tumors and had severe arytenoid edema, which caused airway obstruction (grade 4 late toxicity). However, 1 of these patients developed this condition after radical esophagectomy for secondary esophageal cancer 2 years after the treatment for glottic cancer, which caused recurrent nerve paralysis. This patient became tracheostomy-dependent until he died of another duplicate hypopharyngeal cancer. The other patient developed dyspnea and arytenoid cartilage necrosis 8 months after the completion of RT and was tracheostomy-dependent without evidence of tumor recurrence for 66 months. Exclusion of the entire arytenoid cartilage outside of the 95% RT isodose volume could not be achieved because of the patients build, which necessitated a 3-field beam arrangement (90, 180, and 270 degrees) to achieve adequate coverage of the entire gross tumor volume located near the posterior commissure. Grade 1 laryngeal edema developed in 5 patients (10%) with T2 disease. Among the patients with T1 disease, grade 1 laryngeal edema developed only in 2 patients (2%). As for voice change, most patients recovered from grade 1 hoarseness within a few weeks after treatment and there were no cases of grade 2 or more severe late toxicity. There were no other cases of moderate or severe toxicity and no cases with moderate or severe adverse events after the salvage surgeries.

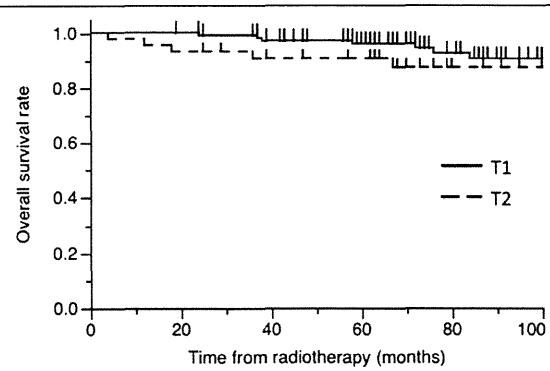

FIGURE 5. Kaplan–Meier estimates of the overall survival. Solid and dashed lines represent patients with T1 and T2 disease, respectively.

Cerebral infarction occurred in 7 patients (5 patients with T1 and 2 patients with T2 tumors). The patients who developed brain infarction ranged in age from 60 to 83 years (median, 74 years). The time from RT to the onset of brain infarction ranged from 44 to 79 months (median, 65 months). However, 1 of these 7 patients had preexisting diabetes mellitus and another had a history of cerebral infarction before the radiation treatment. The cumulative incidence rates of cerebral infarction at 5 and 10 years were 2.4% and 7.5%, respectively.

DISCUSSION

A number of retrospective studies on definitive RT for early glottic cancer have suggested that accelerated fractionation RT could yield better outcomes than RT with conventional fractionation.[1,2,4,8,11,12] Yamazaki et al[8] reported local control rates of 77% and 92% ($p = .004$), respectively, after RT administered by the conventional (2 Gy per fraction) and accelerated fractionation schedules (2.25 Gy per fraction) in patients with T1 glottic cancer, in a randomized study. Mendenhall et al[1] also reported local control rates of 93% to 94% and 72% to 80%, respectively, at 5 years in patients with T1 and T2 tumors receiving accelerated fractionation RT. Similar results after RT using accelerated fractionation have also been reported from other institutions.[1,2,4–8] In theory, the shorter the overall treatment time of RT, the better the expected local control rate, as a result of prevention of accelerated repopulation of tumor cells on the premise that adverse reactions of normal tissue are acceptable.[10,11,14,15] We tested a fractional dose of 2.4 Gy to deliver a total RT dose of >60 Gy in order to achieve a 1-week reduction of the overall treatment time in a

phase II study. At the end of patient accrual for this study, we decided to continue this strategy for patients with early glottic cancer, although there was a concern that all the patients had not been followed up for sufficiently long to allow a final decision to be made on the long-term safety of this fractionation. However, as expected, this retrospective analysis demonstrated acceptable long-term morbidities with 5-year local control rates of 93% and 77% in patients with T1 and T2 disease, respectively, which were almost equal to those reported previously.

The method used for RT planning is another important issue to be considered. In general, cobalt γ-ray or 4 MV X-ray irradiation has been the preferred treatment for early glottic cancer to avoid underdosing, especially at the anterior commissure, because of the build-up phenomenon. However, only 6 MV X-rays were available at our institution and, therefore, bolus material was always used. We did not routinely use wedge compensators to reduce the RT dose to the arytenoid while maintaining sufficient dose delivery to the anterior part of the vocal cords where the epicenter of the disease was located in most of our patients. Given that the local control rate in this study was encouraging and serious adverse events occurred only in patients receiving unusual RT planning or major surgery for a second malignancy, we believe that the reliability of the dose estimation and delivery by the RT system was the most important factor for obtaining satisfactory results.

In patients with T1 disease, the total RT dose was increased from 60 Gy to 64.8 Gy in patients with a high initial tumor volume or slow response to RT. The local control rate was 96% in the 82 patients who had favorable background characteristics. However, the local control rate was decreased in patients who had bulky disease and/or poorly responding tumors to almost a level equal to that in patients with T2 disease. In the latest UICC T classification, glottic cancer invading the paraglottic space on CT images is classified as T3 disease. Because CT-based tumor staging was not routinely performed during this study period, some cases of T3 disease might have been treated as bulky T1 or T2 disease in this study. Current UICC TNM classification defines tumors showing paraglottic space invasion as T3 disease even in the absence of vocal cord fixation, implying that this disease can be a candidate for more intensive treatment, such as concurrent chemoradiotherapy. We are currently using the latest UICC T classification, and the outcomes after accelerated RT according to this classification will be done. Factors influencing the local control rate after RT for early glottic cancer have been reported, such as the fractionation schedule, total dose, treatment era, extent of tumor involvement, field size, beam energy, and overall treatment time.[16–21] It was not possible to analyze these factors because of the uniform backgrounds of the treatment parameters in this group of patients. However, the difference in the local control rates implies that a subgroup of patients with T1 disease are candidates for further study to improve the outcomes through identifying factors related to the intrinsic radioresistance of the tumor cells. It should be noted that none of the patients receiving RT at 64.8 Gy/27 fractions developed grade 2 or worse deterioration of the voice quality or laryngeal function, given that our dose constraint to the arytenoid cartilage was satisfied. Judgment of the tumor volume and response may depend on the policies and experience of each institution and physician. Therefore, administration of a total dose of 64.8 Gy should be positively considered when the tumor is judged as showing unfavorable clinical features.

Twelve of the 16 patients who developed local recurrence underwent successful partial laryngectomy as salvage treatment. The larynx-preservation rates at 5 years were 99% and 95% in the patients with T1 and T2 disease, respectively, comparable to previously reported outcomes.[1,2,4–8] This indicates that larynx-preservation was not compromised even in patients receiving accelerated RT.

Although this retrospective chart review could not reveal the incidence of grade 0 to 2 acute dermal and/or mucosal toxicity in detail, there were no cases of grade 3 or more severe acute toxicity. Typically, acute reactions, including dermatitis with moist desquamation, resulting from the use of bolus materials resolved within 3 weeks of RT if adequate supportive treatment was administered. The incidence of grade 2 or worse acute skin reactions after RT using cobalt and/or 4 MV X-rays as the state-of-the-art equipment should be compared with our results while conducting adequate quality assurance and supportive care. Severe late toxicities (grade 3 or more) were observed in only 1% of the patients, which was also comparable to previous reports.[1,2,4–8] The incidence of cerebrovascular accidents after RT for head and neck cancer has also been a matter of concern.[22–28] The reported incidence of cerebral ischemic stroke after RT to the head and neck area ranges from 2.6% to 19%.[22–28] The cumulative incidence rate of this event at 5 years was 2.4% in this study. Although longer follow-up is required,[29] it seems likely that the benefits of accelerated RT outweigh the risk of cerebrovascular accidents.

Although this retrospective chart review has an inherent bias, the data suggest that accelerated RT for early vocal cord cancer is feasible, with encouraging oncologic and functional outcomes. At present, the Japan Clinical Oncology Group is conducting a randomized prospective study (JCOG0701) to compare conventional fractionation with accelerated fractionation schedules to treat T1/T2 vocal cord cancer. This study may provide more data regarding the safety and efficacy of accelerated RT for early glottic cancer in multi-institutional settings.

ACKNOWLEDGEMENTS

This study was supported in part by the National Cancer Center Research and Development Fund (25-A-10), and also was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (24591863 & 24791341), and by Health Science Research Grants from the Ministry of Health and Welfare.

REFERENCES

1. Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB. Management of T1–T2 glottic carcinomas. *Cancer* 2004;100:1786–1792.

2. Le QT, Fu KK, Kroll S, et al. Influence of fraction size, total dose, and overall time on local control of T1–T2 glottic carcinoma. *Int J Radiat Oncol Biol Phys* 1997;39:115–126.

3. Smee RI, Williams JR, Broadley K, Bridger GP. Early glottic carcinoma treated by radiotherapy: defining a population for surgical salvage. *Laryngoscope* 2013;123:171–176.
4. Thariat J, Bruchon Y, Bonnetain F, et al. Conservative treatment of early glottic carcinomas with exclusive radiotherapy. *Cancer Radiother* 2004;8: 288–296.
5. Hartl DM, Ferlito A, Brasnu DF, et al. Evidence-based review of treatment options for patients with glottic cancer. *Head Neck* 2011;33:1638–1648.
6. Furusaka T, Matuda H, Saito T, Katsura Y, Ikeda M. Long-term observations and salvage operations on patients with T2N0M0 squamous cell carcinoma of the glottic larynx treated with radiation therapy alone. *Acta Otolaryngol* 2012;132:546–551.
7. Garden AS, Forster K, Wong PF, Morrison WH, Schechter NR, Ang KK. Results of radiotherapy for T2N0 glottic carcinoma: does the "2" stand for twice-daily treatment? *Int J Radiat Oncol Biol Phys* 2003;55:322–328.
8. Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *Int J Radiat Oncol Biol Phys* 2006;64:77–82.
9. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006;368: 843–854.
10. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet* 2003; 362:933–940.
11. Rosenthal DI, Ang KK. Altered radiation therapy fractionation, chemoradiation, and patient selection for the treatment of head and neck squamous carcinoma. *Semin Radiat Oncol* 2004;14:153–166.
12. Warde P, O'Sullivan B, Bristow RG, et al. T1/T2 glottic cancer managed by external beam radiotherapy: the influence of pretreatment hemoglobin on local control. *Int J Radiat Oncol Biol Phys* 1998;41:347–353.
13. Kagami Y, Imai A, Ito Y, et al. Safety and effectiveness of radiotherapy using 2.4 Gy/fractions for patients with T1, T2, N0M0 glottic cancer. *Nippon Igaku Houshasen Gakkai Zasshi* 2004;64:S148–S149 abstract.
14. Saarilahti K, Kajanti M, Lehtonen H, Hämäläinen T, Joensuu H. Repopulation during radical radiotherapy for T1 glottic cancer. *Radiother Oncol* 1998;47:155–159.
15. Hall EJ, Giaccia AJ. Radiobiology for the radiologist. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2012. pp 391–411.
16. Marshak G, Brenner B, Shvero J, et al. Prognostic factors for local control of early glottic cancer: the Rabin Medical Center retrospective study on 207 patients. *Int J Radiat Oncol Biol Phys* 1999;43:1009–1013.
17. Narayana A, Vaughan AT, Kathuria S, Fisher SG, Walter SA, Reddy SP. P53 overexpression is associated with bulky tumor and poor local control in T1 glottic cancer. *Int J Radiat Oncol Biol Phys* 2000;46:21–26.
18. van der Voet JC, Keus RB, Hart AA, Hilgers FJ, Bartelink H. The impact of treatment time and smoking on local control and complications in T1 glottic cancer. *Int J Radiat Oncol Biol Phys* 1998;42:247–255.
19. Reddy SP, Mohideen N, Marra S, Marks JE. Effect of tumor bulk on local control and survival of patients with T1 glottic cancer. *Radiother Oncol* 1998;47:161–166.
20. Yu E, Shenouda G, Beaudet MP, Black MJ. Impact of radiation therapy fraction size on local control of early glottic carcinoma. *Int J Radiat Oncol Biol Phys* 1997;37:587–591.
21. Gultekin M, Ozyar E, Cengiz M, et al. High daily fraction dose external radiotherapy for T1 glottic carcinoma: treatment results and prognostic factors. *Head Neck* 2012;34:1009–1014.
22. Chu CN, Chen SW, Bai LY, Mou CH, Hsu CY, Sung FC. Increase in stroke risk in patients with head and neck cancer: a retrospective cohort study. *Br J Cancer* 2011;105:1419–1423.
23. Smith GL, Smith BD, Buchholz TA, et al. Cerebrovascular disease risk in older head and neck cancer patients after radiotherapy. *J Clin Oncol* 2008; 26:5119–5125.
24. Scott AS, Parr LA, Johnstone PA. Risk of cerebrovascular events after neck and supraclavicular radiotherapy: a systematic review. *Radiother Oncol* 2009;90:163–165.
25. Huang YS, Lee CC, Chang TS, et al. Increased risk of stroke in young head and neck cancer patients treated with radiotherapy or chemotherapy. *Oral Oncol* 2011;47:1092–1097.
26. Dorresteijn LD, Kappelle AC, Boogerd W, et al. Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. *J Clin Oncol* 2002;20:282–288.
27. Haynes JC, Machtay M, Weber RS, Weinstein GS, Chalian AA, Rosenthal DI. Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. *Laryngoscope* 2002;112:1883–1887.
28. Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. *Stroke* 2011;42:2410–2418.
29. Rosenthal DI, Fuller CD, Barker JL Jr, et al. Simple carotid-sparing intensity-modulated radiotherapy technique and preliminary experience for T1–2 glottic cancer. *Int J Radiat Oncol Biol Phys* 2010;77:455–461.

Radiol Phys Technol
DOI 10.1007/s12194-015-0308-3

Dose calculation accuracies in whole breast radiotherapy treatment planning: a multi-institutional study

Shogo Hatanaka · Yuki Miyabe · Naoki Tohyama · Yu Kumazaki · Masahiko Kurooka · Hiroyuki Okamoto · Hidenobu Tachibana · Satoshi Kito · Akihisa Wakita · Yuko Ohotomo · Hiroyuki Ikagawa · Satoshi Ishikura · Miwako Nozaki · Yoshikazu Kagami · Masahiro Hiraoka · Teiji Nishio

Received: 8 September 2014 / Revised: 22 January 2015 / Accepted: 22 January 2015

Abstract Our objective in this study was to evaluate the variation in the doses delivered among institutions due to dose calculation inaccuracies in whole breast radiotherapy. We have developed practical procedures for quality assurance (QA) of radiation treatment planning systems. These QA procedures are designed to be performed easily at any institution and to permit comparisons of results across institutions. The dose calculation accuracy was evaluated across seven institutions using various irradiation conditions. In some conditions, there was a >3 % difference between the calculated dose and the measured dose. The dose calculation accuracy differs among institutions because it is dependent on both the dose calculation algorithm and beam modeling. The QA procedures in this study are useful for verifying the accuracy of the dose calculation algorithm and of the beam model before clinical use for whole breast radiotherapy.

Keywords Radiation treatment planning system · Whole breast radiotherapy · Quality assurance · Dose calculation algorithm · Multi-institutional study

1 Introduction

In radiation therapy, the dose delivered to the target is expected to be similar among institutions. Any deficiency

S. Hatanaka (✉)
Department of Radiation Oncology, Saitama Medical University Saitama Medical Center, 1981, Kamoda, Kawagoe City, Saitama 350-8550, Japan
e-mail: hata19840928@gmail.com

Y. Miyabe · M. Hiraoka
Department of Radiation Oncology and Image-applied Therapy, Kyoto University Graduate School of Medicine, 54, Kawahara-Cho, Shogoin, Sakyo-Ku, Kyoto City, Kyoto 606-8507, Japan

N. Tohyama
Department of Radiation Oncology, Tokyo Bay Advanced Imaging and Radiation Oncology Clinic Makuhari, 1-17, Toyosuna, Mihama-Ku, Chiba City, Chiba 261-0024, Japan

Y. Kumazaki
Department of Radiation Oncology, Saitama Medical University International Medical Center, 1397-1, Yamane, Hidaka City, Saitama 350-1298, Japan

M. Kurooka
Department of Radiation Oncology, Kanagawa Cancer Center, 2-3-2, Nakao, Asahi-Ku, Yokohama City, Kanagawa 241-8515, Japan

H. Okamoto · A. Wakita
Department of Radiation Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-Ku, Tokyo 104-0045, Japan

H. Tachibana · Y. Ohotomo
Department of Radiation Oncology, The Cancer Institute Hospital of Japanese Foundation of Cancer Research, 3-8-31, Ariake, Koto-Ku, Tokyo 135-8550, Japan

S. Kito
Department of Radiotherapy, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-Ku, Tokyo 113-8677, Japan

H. Ikagawa
Department of Radiology, Shiga Medical Center for Adults, 5-4-30, Moriyama, Moriyama City, Shiga 524-8524, Japan

S. Ishikura
Department of Radiology, Koshigaya Municipal Hospital, 10-47-1, Higashikoshigaya, Koshigaya, Saitama 343-8577, Japan

Published online: 03 February 2015