generally accepted that a dose–response relationship exists between local tumor control and radiation dose in head and neck cancer, especially for nasopharyngeal cancer (5, 6). Therefore hSRT is a suitable option for boost treatment but few studies have investigated feasibility and clinical outcome (7-10) including CyberKnife (5, 8). Since we have employed the CyberKnife system for a boost treatment for tumors in the head and neck area, we thus reviewed those outcomes as a multi-institutional survey because of the scarce number of patient in each institution.

Patients and Methods

Patients and radiotherapy techniques. Records of patients who treated with CyberKnife hSRT (Accuray, Sunnyvale, CA, USA) at four hospitals (Soseikai General Hospital, Osaka University Hospital, Fujimoto Hayasuzu Hospital, Okayama Kyokuto Hospital) during 2000 and 2010 were reviewed for inclusion into the study. Patients who received hSRT as a planned boost for primary lesion after external radiotherapy were included. They received boost therapy with Cyberknife mainly due to unfavorable condition such as tumors in close proximity to serial organs and/or their comorbidities. Initial radiotherapy was delivered by a conventional technique using a linear accelerator (Linac) and boost hSRT was performed using the CyberKnife systems. Patient included 16 males and 9 females, with age ranged from 18 to 83 years (median, 65 years). Treatment sites were 11 nasopharynx, 7 oropharynx, one hypopharynx, 3 nasal cavity or paranasal sinus (one nasal, one ethmoid sinus and one maxillary sinus) and three oral cancers. All, but three, tumors were histologically confirmed as squamous cell carcinoma. One adenoid cystic carcinoma in nasal cavity, one primitive neuroectodermal tumor in ethmoid and one lymphoepithelioma in nasopharynx were also included. Table I shows the patients' characteristics. The T, N category was identified using the Union for International Cancer Control (UICC) tumor node metastasis (TNM) system, sixth edition (11). All patients underwent preceding conventional radiotherapy of 35 to 72 Gy (median, 50 Gy) in 1.2-Gy (twice a day) to 2-Gy fractions. The dose and fractionation scheme of the Cyberknife SRT boost was individualized and the prescribed dose ranged from 12 Gy to 35 Gy in 1 to 5 fractions (median, 15 Gy in 3 fractions). Involved node was also irradiated until 60 Gy or more by conventional fractionation. The total prescribed dose was summed using the Equivalent dose in 2 Gy fraction formula $EQD2Gy=n\times d\times(\alpha/\beta+d)/(\alpha/\beta+2)$. Basically, chemotherapy were administered in T3< or N2< cases during initial conventional radiotherapy. Cisplatin (*i.e.*, 70-80 mg/m^2/3 weeks) or 5-fluorouracil (5-FU) therapy (*i.e.*, 5-FU at 250 mg/m^2 and cisplatin at 5 mg/m^2 for the initial 3 three weeks) were used. However, some cases did not receive chemotherapy because of their comorbidity or patients will.

Statistical analysis. All statistical analyses were performed using the Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). The percentage values were analyzed using the χ^2 test and means were compared using the Student's *t*-test for normally distributed data and the Mann-Whitney *U*-test for skewed data. Survival data were estimated by the Kaplan–Meier method and examined for significance using the log rank test. Cut-off value was set at average or median value of each variable if otherwise stated. All analyses used the conventional $p<0.05$ level of significance.

Table I. *Patients' characteristics.*

Variable		N
Age (years)	Median (range)	63 (18-83)
Gender	Male	16
	Female	7
Primary site	Nasopharyngeal cancer	11
	Oropharyngeal cancer	7
	Hypopharyngeal cancer	1
	Oral cancer	3
	Nasal and paranasal sinus	3
T category	1	2
	2	8
	3	5
	4	8
	Not available	1
N category	0	15
	1	2
	2	6
	3b	1
	Not available	1
PTV	cm^3	12.8 (1-81)
Initial effect	Complete response	18
	Partial response	6
	Progressive disease	1

PTV, Planning target volume.

Results

Median follow-up time for surviving patients was 28 months (range=7-128 months) after hSRT. There are 18 complete responses, 6 partial responses and one progressive disease, resulted in 96% (24/25) response rate. A 63-year-old male with oropharyngeal cancer showed progressive disease even after 40 Gy in 20 fractions of external-beam radiotherapy combined with a boost of 22 Gy in 3 fractions by CyberKnife. He choked and died 9 months after radiotherapy, although tumor was stable up to that time point. Local control (LC) at 2- and 5-years were 89% and 71%, respectively (Figure 1). Progression-free (PFS) and overall survival (OS) at 2- and 5-years were 70% (83%) and 70% (70%), respectively (Figure 1). No patients showed lymph node recurrence without local failure. Univariate analysis revealed that initial response and planning target volume (PTV) were significant prognostic factors for progression free survival and overall survival (Table II). Patients with a PTV ≤20 cm^3 showed better PFS (92%) and OS (100%) than patients with a PTV >20 cm^3 (61% and 47%, respectively) (Figure 2). Good initial response correlated to better outcome in LC, PFS and OS (Table II).

For toxicity, fistula was seen in two patients. One patient (T4N1 upper gum cancer) showed fistula between nasal cavity and oral cavity with simultaneous recurrent tumor and another patient (T3N0 nasal adenoid cystic cancer) showed

Table II. *Analysis of prognostic factors after CyberKnife boost therapy.*

				At 2 years				
Variable	Strata	N	LC	*p*-Value	PFS	*p*-Value	OS	*p*-Value
Age, years	65 or more	12	83%	0.779	68%	0.75	92%	0.41
	<65	13	92%		75%		74%	
Gender	Male	16	87%	0.87	75%	0.88	73%	0.098
	Female	9	80%		64%		100%	
T Category	-T3	18	87%	0.28	77%	0.24	89%	0.41
	T4	7	83%		48%		64%	
N category	0	19	87%		73%	0.73	72%	NA
	1-	6	100%		44%		100%	
Location	Nasopharynx	11	89%	0.38	80%	NA	89%	0.38
	Oropharynx	7	57%		71%		71%	
	Hypopharynx	1	100%		100%		67%	
	Oral	3	100%		33%		67%	
	Nasal and paranasal cavity	3	50%		50%		100%	
PTV volume	≤20 cm^3	13	100%	0.1	92%	0.027	100%	0.015
	20 cm^3<	11	81%		47%		61%	
Total prescribed dose	≤80Gy	13	100%	0.23	84%	0.22	92%	0.63
(EQD2Gy:α/β=10)	80Gy<	12	71%		58%		75%	
Tumor response	Complete response	18	100%	<0.0001	83%	<0.0001	100%	0.0037
	Partial resonse	6	40%		33%		44%	
	Progressive disease	1	0%		0%		0%	

LC, Local control; PFS, progression free survival; OS, overall survival, EQD2Gy, Equivalent dose in 2 Gy fractions.

fistula into the oral cavity with necrosis after re-treatment for recurrent tumor. These toxicities occurred with and were considered owned to concurrent recurrent tumors. No toxicity more than grade 3. Grade 2 reactions included 3 mild ulcerations, one bleeding and one hearing loss.

Discussion

Because of the vicinity of the tumor to neighboring critical structures (*e.g.*, brainstem and optic apparatus), dose-escalation with conventional external-beam radiation therapy (EBRT) and/or brachytherapy is limited by the radiation tolerance of the adjacent normal tissues. Recently, the use of intensity-modulated radiotherapy (IMRT), which allows for higher tumor dose delivery, while sparing the surrounding normal tissues, resulted in excellent LC and acceptable toxicity rates at selected institutions, suggesting that dose escalation is feasible with accurate tumor targeting (5). Stereotactic radiosurgery has been used for many years as an effective treatment for intracranial tumors. The dose distribution provided by radiosurgery for large or advanced tumors is more homogeneous and thereby can spare more normal tissues than brachytherapy or EBRT (5). Lee *et al.* reported an excellent LC, 100% at 3 years, with acceptable late toxicities in 45 patients with nasopharyngeal cancer who received boost radiotherapy; out of those, 12 patients were treated using the

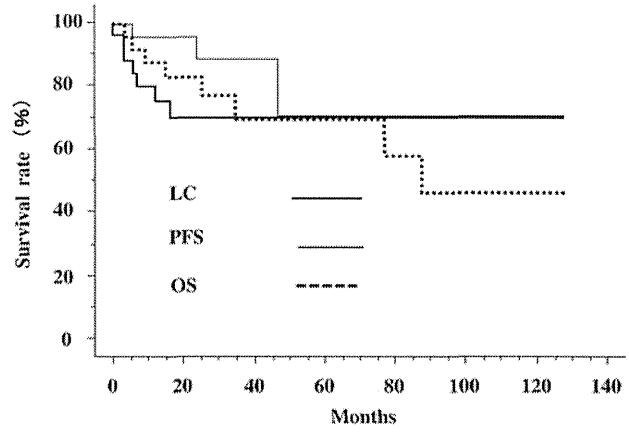

Figure 1. *Local control (LC), progression-free survival (PFS) and overall survival (OS) rates for all patients. The thick line depicts LC rate, thin line depicts PFSrate and dotted line depicts OS rate.*

CyberKnife with a median dose of 12 Gy delivered in a single fraction after a median total dose of 66 Gy by conventional radiotherapy, with an interval of 4-8 weeks.

Al-Mamgani *et al.* reported boost treatment outcome for oropharyngeal cancers (12) by means of CuberKnife hSRT (3-times 5.5 Gy, prescribed to the 80% isodose line), after 46 Gy of IMRT to the primary tumor and neck (when

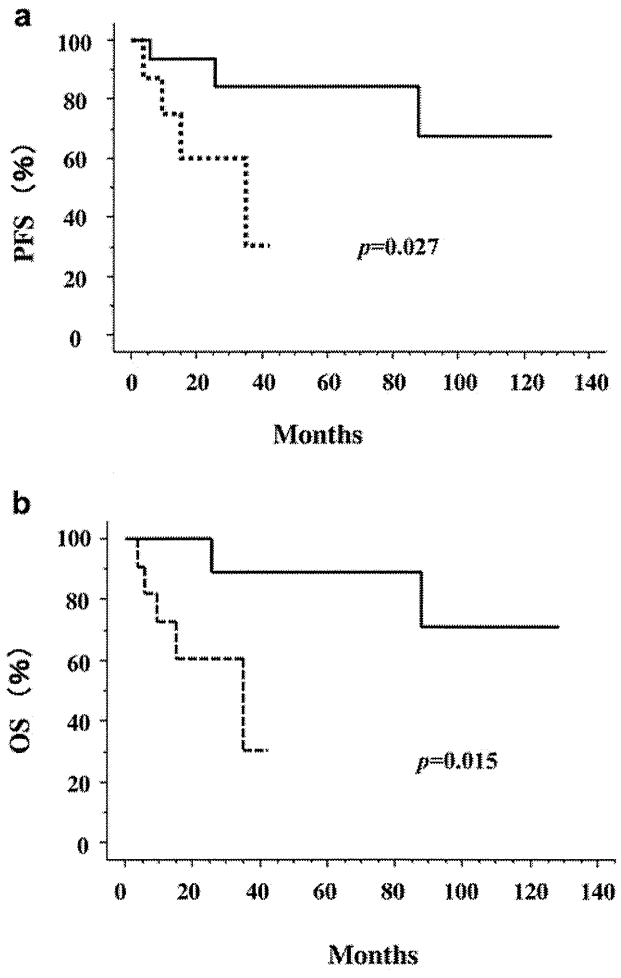

Figure 2. *Progression-free survival (PFS) and overall survival (OS) rates according to planning target volume (PTV). Patients with PTV ≤20 cm^3 (thick line) showed better PFS rate (92%) and OS rate (100%) than patients with PTV >20 cm^3 (dotted line) (61%, p=0.027 and 47% p=0.015, respectively).*

indicated). Between 2005 and 2010, 51 patients with Stage I-IV oropharyngeal cancer received boosts. After a median follow-up of 18 months (range, 6-65 months), the 2-year actuarial rates of LC, PFS and OS were 86%, 80% and 82%, respectively, and the 3-year rates were 70%, 66% and 54%, respectively. Furthermore, the authors of this work accumulated experience in 102 T1-2 oropharyngeal carcinoma patients. The 3-year actuarial incidence of LC was 97%. The figures for PFS and OS were 92% and 81%, respectively (13). The incidence of tube feeding were 17% and 20%, respectively. The figures for grade >2 late dysphasia were 11% and 8% and for xerostomia were 16% and 12%, respectively. These were fairly good outcomes and concurred to our data.

It is interesting and plausible that PTV could be identified as a prognostic factor for PFS and OS. Initial tumor volume is a well-known determinant of prognosis after radiotherapy (14). Tumor volume during radiotherapy reflected tumor response to initial radiotherapy and was also a good indicator for treatment outcome (15). It is also natural that initial response correlated to outcome. Patients with better tumor initial response could enjoy longer survival. Complete response (CR) cases seemed to show smaller PTV (20.3±25 cm^3) than partial response (PR) cases (30.7±14.6 cm^{3}cc) or progressive disease (PD) cases (33.4 cm^3, not significant).

This study had several limitations. First, we analyzed a small patient group from heterogenic disease sites with a short follow-up period. Therefore, it is difficult to determine appropriate schedules for CyberKnife boost treatment. Second, timing, species and dosage of chemotherapy were heterogeneous and thus difficult to analyze. Finally, lymph node status is an important predisposing factor, however, it is difficult to address this issue because we only focused on local boost therapy.

In conclusion, our results showed potential benefits of the CyberKnife SRT boost. Smaller PTV and good initial response predict good outcome after CyberKnife boost treatment.

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Frequency and Predisposing Factors for Interfractional Rectal Displacement Requiring Repeated Precaution in Prostate Cancer Patients Treated with Image-Guided Intensity-Modulated Radiation Therapy

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Abstract. *Aim: To investigate the frequency and characteristics of interfractional rectal displacement in patients with prostate cancer treated with image-guided intensity-modulated radiation therapy (IG-IMRT) using helical tomotherapy. Patients and Methods: Data for a total of 256 patients were analyzed. Megavoltage computed tomography (MVCT) images were acquired before radiation therapy and interfractional rectal displacement was assessed with soft-tissue matching by comparing treatment planning images within 9,445 fractions. Anterior rectal region displacement larger than 5 mm, requiring repeated precaution, was defined as the action level of rectal displacement (ARD). Results: ARD was identified in 676 (7.2%) out of 9,445 fractions and at least once in 75% (190/256) of patients. Univariate analysis identified three predisposing factors for ARD: body mass index (BMI), rectal volume and prostate volume. Multivariate logistic regression analysis revealed that lower BMI and large rectal volume were statistically significant predictors of ARD. The highest incidence of ARD (13.6% and 9.1%) was found during the initial two weeks of treatment (first five and next five fractions), after which the incidence decreased to 5.96% ($p<0.0001$). Conclusion: ARD was identified in 7.9% of fractions and in 74.8% of patients and was most likely to occur in patients with a low BMI and/or large rectal volume. ARD occurred predominantly during the initial two weeks of treatment and became less likely over time.*

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Key Words: Tomotherapy, prostate cancer, organ dislocation, image-guided IMRT, MVCT.

Radiation therapy is one of the most widely used treatments for localized prostate cancer. With the development of radiation techniques, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), it is possible to deliver higher prescribed doses with few serious adverse reactions (1). This process enables the delivery of accurate radiation therapy with a reduction in the size of the set-up margin and, therefore, a smaller planned target volume (PTV) (2). Helical tomotherapy is a form of IMRT with the ability to acquire megavoltage computed tomography (MVCT) images of a patient in the treatment position before therapy. This precise positioning using CT images allows not only for correct bone position (bone matching) used in conventional radiation therapy and suitable for bone lesions (2) but also for the visualization and identification of the position of organs, such as the prostate, rectum and bladder (soft-tissue matching). In our Unit, we identified interfractional rectal displacement using repeated MVCT before treatment and correct patient positioning using couch adjustment, a process known as image-guided IMRT (IG-IMRT) (3-6). However, we sometimes encountered considerable rectal displacement, which is sometimes impossible to correct using couch adjustment. We define this degree of displacement as the action level of rectal displacement (ARD). In these cases, the patient gets up from the couch and is instructed to drink water to fill the bladder and/or to void the rectum. A rectal enema is prescribed in several cases. The aim of the present study was to analyze the characteristics and predisposing factors for ARD, because ARD may not only cause treatment failure and/or toxicities but also be a bothersome phenomenon both for medical staff and patients.

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Patients and Methods

Patients and patients' management. We investigated 256 male patients with prostate cancer who received IG–IMRT using helical tomotherapy (HI-ART TomoTherapy Inc., Madison, WI, USA) between 2009 and 2013. The patients were aged between 48 and 86 years (median=72 years). The patients' characteristics are presented in Table I. Details of the treatment have been described elsewhere (3, 4). In brief, vacuum cushions (Blue Bag, Medical Intelligence, Schwabmûenchen, Germany) were used to immobilize the patients in the supine position. Kilovoltage CT planning images were acquired for each patient (2-mm slice thickness), including a minimum of 5 cm above and below the level of the PTV (Aquilion 64; Toshiba Medical Systems Inc., Tokyo, Japan). The prostate gland and seminal vesicles were contoured as the clinical target volume (CTV) with the aid of fused magnetic resonance imaging (MRI) images. The primary PTV was defined by margins of 3 mm posteriorly and 5 mm in all other dimensions around the prostate gland and seminal vesicles (4). The prescribed dose was 72 Gy in 36 fractions for patients in the low-risk group and 74 Gy in 37 fractions for patients in other risk groups, set as D95 (*i.e.*, 95% of the PTV received the prescribed dose). The bladder and rectum (contoured from anal verge to rectosigmoid junction) were defined as risk organs and the major constraints during inverse planning were that no more than 35% of the rectal volume and no more than 50% of the bladder volume would receive 40 Gy of radiation. Patients were routinely instructed to empty the rectum, but not the bladder, 1 h before treatment. Patients took magnesium oxide (1 g/day) and dimethicone (80 mg 3 times a day, a total of 240 mg/day) 7 days prior to planning CT until the completion of treatment. If necessary, the dosage was altered according to patient response. MVCT images (3.5 MV) were acquired through PTV before treatment delivery, with a minimum slice thickness of 4 mm and a field of view of 35 cm. The first MVCT images were taken and autofused with the kilovoltage CT treatment planning images, and the superior–inferior, anterior–posterior and right–left shifts were then calculated using automatic image fusion for bone matching. The fused images were manually inspected for prostate soft-tissue matching and verified and corrected by two clinicians (rotational corrections were not implemented at the time of this study). Patients were then shifted into the calculated position by adjusting the couch. We defined ARD if most anterior rectal region moved larger than 5 mm and could not be corrected using couch adjustment (Figure 1). In these cases the patient was asked to get up from the couch and to void the rectum. If necessary, a rectal enema was used to dislodge large-volume rectal stool and/or rectal gas. A second set of MVCT images were acquired to verify that the prostate shift had been corrected. If ARD persisted, further correction was implemented. The total time between image acquisition and treatment delivery was typically less than 10 min. However, if ARD occurred, the time delay could be in the range of hours. We investigated the frequency and characteristics and predisposing factors for ARD.

Statistical analysis. All statistical analyses were performed using the Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). The percentage values were analyzed using the χ^2 test and means were compared using the Student's *t*-test. Variables that had *p*-values <0.10 were tested further in multivariable analysis using a logistic regression model. All analyses used the conventional $p<0.05$ level of significance.

Table I. *Patients' characteristics.*

Variables		No. or median (range)
Age	(years)	72 (48-86)
Height	(m)	1.65 (1.5-1.85)
Body weight	(kg)	62 (42-95)
Body mass index	(kg/m^2)	23.3 (14.9-30.5)
Dose / fractions	74 Gy/37 fractions	229
	72 Gy/36 fractions	27
T category	T1:T2:T3a:T3b:T4:NA	79:108:50:13:3:3
Planned target volume (PTV)	(cm^3)	84.3 (31.6-217.6)
Prostate volume	(cm^3)	39.9 (15.5-136.)
Bladder volume	(cm^3)	158.9 (45.2-488.8)
Rectal volume	(cm^3)	40.9 (19.5-198.3)

Results

We treated 256 patients with 72 Gy/36 fractions (27 patients) or 74 Gy/37 fractions (229 patients). In total, 9,445 fractions and 10,279 MVCT images were analyzed for deviations of the prostate using soft-tissue matching. ARD occurred in 676 fractions (7.2%) out of 9,445 fractions (median, 2 ARD fractions in a patient; range, 1-15 ARD fractions in a patient). During the treatment course with 36-37 fractionations, 54 patients experienced 1 ARD, 27 two ARD, 35 three ARD, 24 four ARD and 51 five or more ARD during the treatment course. 75% (190/256) of patients experienced ARD at least once.

The highest incidence of ARD (13.6% and 9.1%) was found during the initial two weeks of treatment (first five and next five fractions), after which the incidence decreased to 5.96% (Table II) ($p<0.0001$). 137 patients (54%) showed ARD twice or more during treatment fractions. The predisposing factors for ARD are presented in Table III. Univariate analysis identified three predisposing factors for ARD: body mass index (BMI), rectal volume and prostate volume. The 191 patients with ARD had lower BMI (22.9±2.79 kg/m^2), larger prostate volume (44.9±18.7 cm^3) and larger rectal volume (44.8±16.5 cm^3) than their 65 counterparts (BMI 23.7±2.5 kg/m^2, prostate volume 39.5±13.5 cm^3 and rectal volume 37.9±10.9 cm^3). Multivariate logistic regression analysis revealed that BMI (odds ratio (OR)=0.404, 95% Confidential interval (95% CI)=0.201-0.815, $p=0.0113$) and rectal volume (OR)=3.458, 95% CI=1.949-6.468, $p=0.0001$) were identified as statistically significant predisposing factors for ARD (Table IV).

We examined the background characteristics of 51 patients with particularly high frequent occurrence of ARD (≥5 fractions during 36–37 fractions: 20%). BMI (OR=0.300, 95% CI=0.158-0.572, $p=0.0003$) and rectal volume (OR=2.553, 95% CI=1.297-5.065, $p=0.0068$) were identified as predisposing factors causing frequent occurrence of ARD.

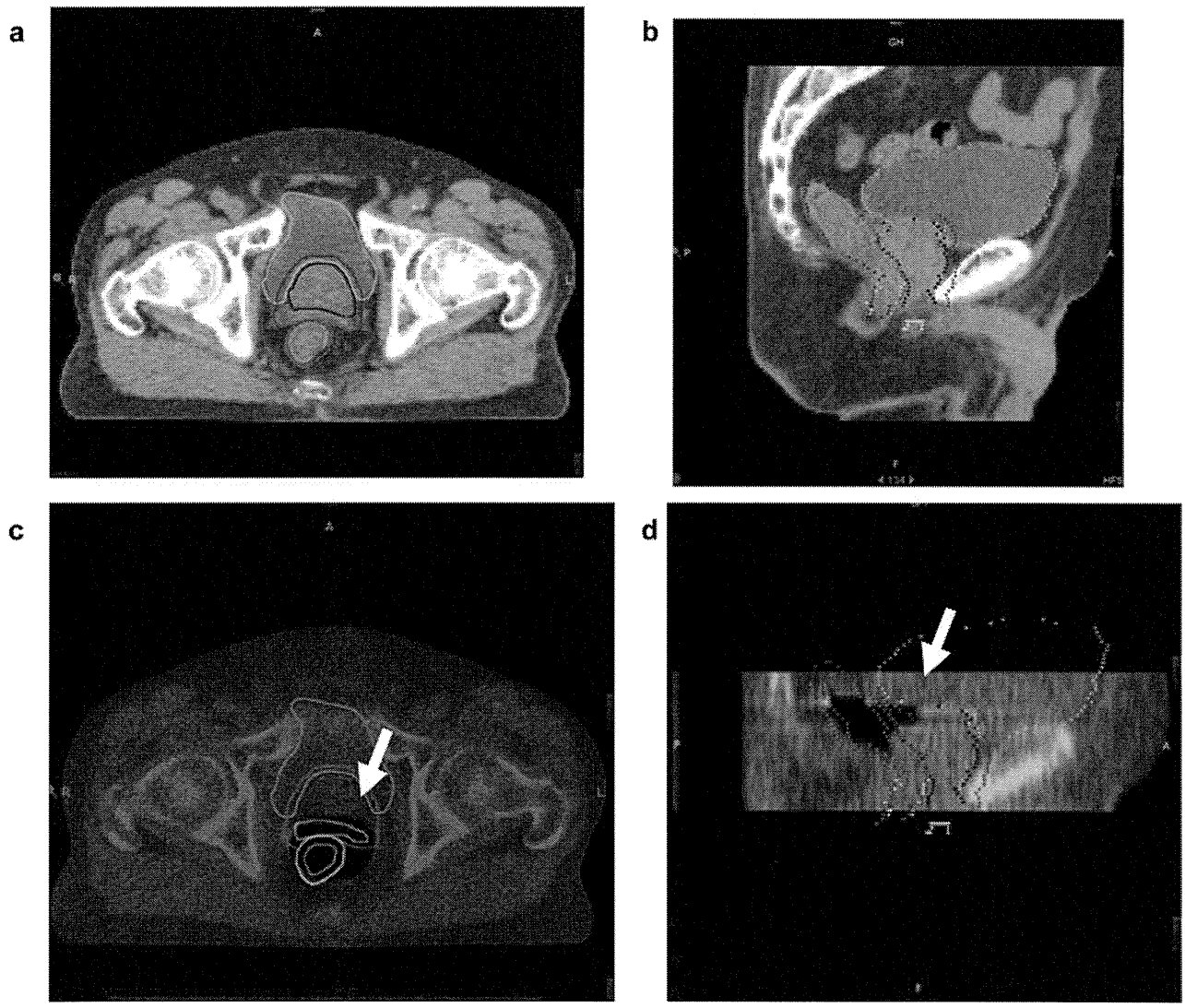

Figure 1. *Scheme of action level of rectal dislocation (ARD) required rectal voiding. a) Axial planning CT images (kVCT) and contour of organ at risks, b) saggital planning CT images (kVCT) and contour of organ at risks, c) axial MVCT image. At the first MVCT scan, this patient's rectum, showed large volumes of gas. Note displacement of rectal contour ≥5 mm compared to previous planning CT images. Arrow indicates rectal gas expansion into PTV, d) Sagittal MVCT image. Arrows indicate rectal gas expansion.*

Discussion

The use of IGRT facilitates precise target location from bone-structure matching to soft-tissue matching. This is particularly important in radiotherapy of prostate cancer because the position of the prostate gland varies with the filling and emptying of the bladder and rectum (7). Several correctional strategies, including implanted fiducials (8) and online three-dimensional CT imaging (9), have been developed and clinically implemented. Prostate matching was not possible in the bone matching era as a result of the lack of soft-tissue contrast in portal images (10-13). Previous studies have revealed that bone matching required PTV margins of 4.7-10.5 mm, 7.4-12 mm and 1.4-4.4 mm in the AP, SI, and LR dimensions, respectively (14-15). Soft tissue matching IG–IMRT enables the use of smaller PTV margins compared to bone matching IMRT (4-6). Several authors, including a researcher from our Institution (4) have assessed intrafractional prostate motion and reported that a 3-5 mm intrafractional margin was adequate for prostate dose coverage, except for seminal vesicle dose coverage (5, 6, 14, 15).

Table II. *Occurrence of action level of rectal displacement (ARD) according to treatment time course.*

	Number of ARD	Total fraction number	(%)	*p*-Value
Initial week (1-5 fractions)	174	1280	13.6%	<0.0001
Second week (6-10 fractions)	116	1280	9.1%	
Third week (11 fractions)-	386	6885	5.6%	

Table III. *Risk factor for action level of prostate displacement (ARD).*

		ARD (–) (n=65)	ARD (+) (n=191)	*p*-Value
Age	(years)	72±6	72±6	0.73
Height	(m)	1.65±0.05	1.65±0.06	0.35
Body weight	(kg)	64.4±6.87	62.6±9.37	0.25
Body mass index	(kg/m^2)	23.7±2.50	22.9±2.79	0.035
Dose/fractions	74 Gy/37 fractions	62	167	0.1
	72 Gy/36 fractions	3	24	
T category	T:;T2:T3:T4:NA	20:31:13:0:1	59:77:50:3:2	0.65
Prostate volume	(cm^3)	39.5±13.5	44.9±18.7	0.0327
Planned target volume (PTV)	(cm^3)	83.9±26.4	95.8±48.2	0.06
Bladder volume	(cm^3)	174±70.8	187±133	0.45
Rectal volume	(cm^3)	39.9±10.9	44.8±16.5	0.0021

The mean and standard deviation (SD).

Table IV. *Results of multivariate logistic regression model for action level of rectal displacement (ARD).*

Variable		Multivariate analysis (*p*-value)	
		ARD (n=191)	ARD ≥5 fractions (n=52)
Body mass index (kg/m^2)	<22 *vs.* 22-	0.0113	0.0003
		OR: 0.404	OR:0.300
		95%CI: 0.201-0.815	CI:0.158-0.572
Prostate volume (cm^3)	<40 *vs.* 40-	0.2049	0.3402
Planning target volume (PTV) (cm^3)	<94 *vs.* 94-	0.0683	0.4066
Rectal volume (cm^3)	<40 *vs.* 40-	0.0001	0.0068
		OR: 3.458	OR: 2.563
		CI: 1.949-6.468	CI: 1.297-5.065

OR, Odds ratio; 95%CI, 95% confidential interval.

On the other hand, MVCT occasionally revealed irregular rectal morphological changes (*e.g.*, partial rectal expansion; Figure 1), which was sometimes impossible to correct using couch adjustment. Our results demonstrated that patients with large rectal volume and/or low BMI were more likely to show rectal displacement. Large rectal volume identified on planning CT images has previously been reported as a predisposing factor for rectal bleeding or prostate-specific antigen (PSA) failure (16, 17). This could be partly explained by our finding that larger rectal volume correlated with frequent prostate displacement during radiotherapy. Stasi *et al.* also pointed out the importance of rectal volume control before and during radiotherapy (18). In the present study, a lean body (low BMI) was also identified as an important predisposing factor for ARD. To our knowledge, this is the first documentation of this finding in the literature. The increased occurrence of the ARD in patients with low BMI may be because lean patients have a small amount of abdominal muscles and/or supporting tissue, allowing for free movement of organs if not adequately corrected during

preparation for treatment. It is plausible that ARD occurs more frequently during the first week of treatment and then decreases, because patients get used to the process of radiotherapy over time. Patients are tense and anxious during the first week but, as they become accustomed to radiotherapy, the muscles tend to become more relaxed.

There are several limitations to the present study. At first, this is a single-institutional retrospective analysis with limited experiences for soft-tissue matching IG-IMRT. Next, we did not use several procedures that have been reported to reduce rectal movement, such as hydrogel spacers (20) or rectal enemas (18, 21). This is probably the reason we initially experienced a few rectal bleeding cases after enema in patients with hemorrhoid; however, it is not totally justified. At last, we could not assess real time rectal movement during irradiation. These problems were left for further research.

In conclusion, ARD occurred most frequently during the initial two weeks of treatment and became less likely over time. Particular caution is required for patients with low BMI/or larger rectal volume.

Conflicts of Interest

The Authors state no conflicts of interest.

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High-dose-rate interstitial brachytherapy in combination with androgen deprivation therapy for prostate cancer

Are high-risk patients good candidates?

External beam radiotherapy (EBRT), interstitial brachytherapy (ISBT) and the combination of both are effective radiotherapeutic treatment modalities for clinically localized prostate cancer. ISBT is particularly useful for delivering high-dose radiation to the prostate gland without increasing doses to the surrounding normal tissues. ISBT can be administered in the following two ways: low-dose-rate (LDR) permanent seed implantation and high-dose-rate (HDR) temporal implantation. HDR-ISBT has some merits, such as a stepping source and dose optimization to improve target coverage after implantation. Furthermore, HDR-ISBT has a radiobiological advantage because the α/β value is lower in the malignant tissue than in the late-responding normal tissue, thereby resulting in superiority of the hypofractionation schedule. In contrast, HDR-ISBT has the disadvantage of prolonged discomfort due to applicator implantation, which decreases the patient's quality of life. Therefore, HDR-ISBT is commonly used as a boost therapy after EBRT [4, 10, 15, 22]. Although several recent studies have indicated that HDR-ISBT monotherapy achieved good biochemical control—even in high-risk patients [7, 27, 32]—this finding remains controversial [11]. We introduced HDR-ISBT as monotherapy more than a decade ago [23–25, 28–30]. In this study, we present our results of treatment with HDR-ISBT and androgen deprivation therapy (ADT) in a retrospective analysis, with a special focus on high-risk patients.

Patients and methods

Patient characteristics

Between July 2003 and June 2008, a total of 113 patients received HDR-ISBT at the National Hospital Organization Osaka National Hospital. The 3 patients who were lost to follow-up before 12 months after HDR-ISBT were excluded from this study. The median age of the 110 included patients was 73 years (range 52–86 years) and median follow-up duration was 71 months (range 12–109 months).

Pretreatment staging included digital rectal examination, computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy. Using the National Comprehensive Cancer Network (NCCN) risk group classification, 17, 45 and 48 patients were classified as low-risk, intermediate-risk and high-risk, respectively. In this study, 48 high-risk patients, including 9 very high-risk patients, were investigated (**Table 1**).

Of the 48 high-risk patients, 6 were classified as having stage T1 disease, 23 as T2, 18 as T3 and 1 patient as T4 according to the 2002 NCCN classification criteria. Histological examination of all patients confirmed adenocarcinoma. Gleason scores (GS) were <7 in 7 patients, 7 in 19 patients, >7 in 20 patients and unknown in 2 patients. The median percentage of positive biopsies was 50 % (range 10–100 %). Perineural invasion was observed in 3 patients. The median pretreatment prostate-specific antigen (PSA) level was 25.1 ng/mL (range 3.8–98.6 ng/mL).

ADT was administered to all 48 patients as a neoadjuvant treatment for a median duration of 8 months (range 3–22 months). Maximal androgen blockade was performed in 37 patients. In addition, 12 patients received adjuvant ADT for a median period of 24 months (range 10–36 months). Patients who were

Table 1 Patient characteristics

Characteristic	Value
Median age (years; range)	72 (52–81)
Median follow-up period (months; range)	73 (12–109)
Gleason score	
≤6 (n)	7
7 (n)	19
≥8 (n)	20
Unknown	2
T stage	
T1–2a (n)	6
T2b–c (n)	23
T3–4 (n)	19
Prostate-specific antigen (PSA)	
Median initial PSA (ng/mL, range)	25.1 (3.8–98.6)
<10 ng/mL (n)	6
10–20 ng/mL (n)	10
>20 ng/mL (n)	32
Dose/fraction (Gy/fractions)	
38 Gy/4 fractions (n)	1
49 Gy/7 fractions (n)	34
54 Gy/9 fractions (n)	13
Androgen deprivation therapy	
Median duration (months, range)	8 (3–45)
Neoadjuvant alone (n)	36
Neoadjuvant and adjuvant (n)	12

T3 (7 patients) or GS ≥ 8 (6 patients) or iPSA > 20 (6 patients) are included. Total treatment duration for the 48 patients was a median of 8 months (range 3–45 months). Seventeen patients received ADT for >12 months.

Applicator implantation

The applicator implantation procedure has been previously described elsewhere [23, 24]. In brief, implantation was performed under lumbar anesthesia. And, epidural anesthesia was continued until applicator extraction. We adopted metal needle applicators for the first 5 patients and flexible needle applicators (ProGuide Sharp Needle®, Nucletron an Elekta Company, Veenendaal, Netherlands) for the remaining 43 patients. We implanted 9–15 (median 13) applicators. In the first 15 patients, this was performed via an nonambulatory implant technique using a nonremovable template (Taisei Medical, Osaka, Japan) for guidance. In the remaining 33 patients, the applicators were implanted using a removable template (Taisei Medical), or by hand, with an ambulatory implant technique [23]. A 6F flexible applicator was used in the ambulatory implant technique. A colored bead was fixed to the applicator using an adhesive; the length between the needle tip and the bead is color-coded (for example, purple bead: 12 cm; green bead: 13 cm; orange bead: 14 cm). After bead fixation, we applied a color button with thread to the side of the bead with a tip. Subsequently, we tightly sutured the button to the patient's perineal skin using thread. Guided by transrectal ultrasonography (SSD-1000® and Prosound α7®, Hitachi Aloka Medical, Ltd., Tokyo, Japan), we implanted the treatment applicator in and around the prostate gland and proximal seminal vesicles (SVs). To prevent dorsal SV displacement near the rectum, we implanted a dummy needle at the template hole that was one template hole dorsal to the hole we initially judged as adequate. This dummy needle ventrally displaced the SV. After the dummy needle was implanted, we implanted the true applicator into the template hole immediately ventral to the one initially judged to be adequate. If the applicator position was considered to give good SV coverage, the dummy needle was extracted [24]. The top 2–3 cm of the applicators were placed within the urinary bladder to allow the planning target volume (PTV) to include a 10-mm margin added to the clinical target volume (CTV) in the cranial direction. This margin was established for the prevention of caudal displacement of the applicators [25]. This technique is similar to those described in other Japanese reports [9, 27].

Treatment planning

After applicator implantation, we performed the treatment planning. CT scans were obtained for all patients and MRI was performed for the 43 patients treated with flexible needle applicators and nonmetallic stoppers. CT-based planning with or without MRI-assistance using the PLATO® and Oncentra® Brachy treatment planning systems (Nucletron) was performed with manual modification [26].

The planned prescribed dose was 54 Gy in 9 fractions over 5 days for the first 13 patients and 49 Gy in 7 fractions over 4 days for the remaining 34 patients. Only 1 patient who was >80 years old was administered 38 Gy in 4 fractions over 3 days. CTV was calculated for the prostate gland and the medial side of the SVs. A 10-mm cranial margin was added to the CTV to generate the PTV. The median dose nonuniformity ratio was 0.32 (range 0.23–0.40).

The treatment machine used was the microSelectron-HDR® (Nucletron). One hour before each irradiation fraction, a urinary balloon catheter was clamped in place to keep the urine within the urinary bladder so that the cranial side of the bladder wall and the rectosigmoid colon were kept away from the irradiation field [9, 27]. Beginning in May 2007, corrective action for applicator displacement was initiated in 10 patients after performing daily CT [20].

Statistical analysis

Statistical analyses were performed using the StatView v. 5.0 (SAS Institute, Cary, NC, USA) software program. We analyzed biochemical control and survival rates using the Kaplan–Meier method. A probability (p) value of <0.05 was considered statistically significant for the log-rank test and dose-volume histogram (DVH) analysis using the Mann–Whitney method.

Results

All 48 patients received the planned treatment dose. The 5-year overall survival rate was 98%. The 5-year biochemical control rate was 87% (**Fig. 1**). A total of 4 patients died: 1 patient succumbed to bone metastasis of prostate cancer and 3 died from intercurrent diseases. Of the 7 patients exhibiting biochemical failure, this was observed within 60 months in 6 cases (86%). One instance of biochemical failure was judged as a case of transient PSA bounce and the patient's prostate-specific antigen (PSA) level decreased without treatment. No clinically apparent inci-

Abstract · Zusammenfassung

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High-dose-rate interstitial brachytherapy in combination with androgen deprivation therapy for prostate cancer. Are high-risk patients good candidates?

Abstract

Background and purpose. To evaluate the effectiveness of high-dose-rate interstitial brachytherapy (HDR-ISBT) as the only form of radiotherapy for high-risk prostate cancer patients.

Patients and methods. Between July 2003 and June 2008, we retrospectively evaluated the outcomes of 48 high-risk patients who had undergone HDR-ISBT at the National Hospital Organization Osaka National Hospital. Risk group classification was according to the criteria described in the National Comprehensive Cancer Network (NCCN) guidelines. Median follow-up was 73 months (range 12–109 months). Neoadjuvant androgen deprivation therapy (ADT) was administered to all 48 patients; 12 patients also received adjuvant ADT. Maximal androgen blockade was performed in 37 patients. Median total treatment duration was 8 months (range 3–45 months). The planned prescribed dose was 54 Gy in 9 fractions over 5 days for the first 13 patients and 49 Gy in 7 fractions over 4 days for 34 patients. Only one patient who was over 80 years old received 38 Gy in 4 fractions over 3 days. The clinical target volume (CTV) was calculated for the prostate gland and the medial side of the seminal vesicles. A 10-mm cranial margin was added to the CTV to create the planning target volume (PTV).

Results. The 5-year overall survival and biochemical control rates were 98 and 87 %, respectively. Grade 3 late genitourinary and gastrointestinal complications occurred in 2 patients (4 %) and 1 patient (2 %), respectively; grade 2 late genitourinary and gastrointestinal complications occurred in 5 patients (10 %) and 1 patient (2 %), respectively.

Conclusion. Even for high-risk patients, HDR-ISBT as the only form of radiotherapy combined with ADT achieved promising biochemical control results, with acceptable late genitourinary and gastrointestinal complication rates.

Keywords

Survival · Radiotherapy · Quality of life · Toxicity · Monotherapy

Hochdosierte interstitielle Brachytherapie in Kombination mit einer Androgendeprivationstherapie beim Prostatakarzinom. Sind Hochrisiko-Patienten gute Kandidaten?

Zusammenfassung

Hintergrund und Zweck. Beurteilung der Wirksamkeit von interstitieller Brachytherapie mit Hochdosisraten („high-dose-rate interstitial brachytherapy", HDR-ISBT) als einzige Form der Radiotherapie für Hochrisiko-Prostatakarzinompatienten.

Patienten und Methodik. Zwischen Juli 2003 und Juni 2008 werteten wir retrospektiv die Ergebnisse von 48 Patienten mit hohem Risiko aus, die im National Hospital Organization Osaka National Hospital mittels HDR-ISBT behandelt worden waren. Die Klassifikation der Risikogruppen wurde gemäß der Richtlinien des „National Comprehensive Cancer Network" (NCCN) durchgeführt. Die mittlere Nachbeobachtungszeit betrug 73 Monate (Bereich 12–109 Monate). Eine neoadjuvante Androgendeprivationstherapie (ADT) erhielten alle 48 Patienten, darunter 12 Patienten zusätzlich als adjuvante Behandlung. Einer maximalen Androgenblockade unterzogen sich 37 Patienten. Die Gesamtbehandlungszeit umfasste im Mittel 8 Monate (Bereich 3–45 Monate). Die geplante vorgeschriebene Dosis betrug bei den ersten 13 Patienten 54 Gy in 9 Fraktionen über 5 Tage bzw. bei den anderen 34 Patienten 49 Gy in 7 Fraktionen über 4 Tage. Nur ein einziger Patient im Alter von über 80 Jahren erhielt eine Dosis von 38 Gy in 4 Fraktionen über 3 Tage. Das klinische Zielvolumen (CTV) wurde für die Prostatadrüse und die mediale Seite der Samenblase (SV) berechnet. Ein 10 mm breiter kranialer Rand wurde dem CTV als Planzielvolumen (PTV) hinzugefügt.

Ergebnisse. Die Gesamtüberlebensrate und die biochemische Kontrollrate über 5 Jahre betrug 98 bzw. 87 %. Späte Grad-3-Urogenital- und -Gastrointestinalkomplikationen traten bei 2 bzw. 1 Patienten (4 bzw. 2 %) auf, während späte Grad-2-Urogenital- und -Gastrointestinalkomplikationen bei 5 bzw. 1 Patienten (10 bzw. 2 %) festgestellt wurden.

Schlussfolgerung. Auch bei Hochrisiko-Patienten erzielte die HDR-ISBT als alleinige Form der Radiotherapie in Kombination mit ADT vielversprechende biochemische Kontrollergebnisse mit akzeptablen späten urogenitalen und gastrointestinalen Komplikationsraten.

Schlüsselwörter

Überleben · Radiotherapie · Lebensqualität · Toxizität · Monotherapie

dence of local recurrence was observed in the other 6 patients with biochemical failure. Two patients showed bone metastasis, but no clinical tumors were detected in the other 4 patients who restarted ADT.

The 5-year biochemical control rates for each tumor-defining factor were as follows: 100, 87 and 84 % for stages T1–2a, T2b–c and T3–4, respectively; 100, 94 and 75 % for GS <7, 7 and >7, respectively ($p = 0.002$); 100, 70 and 90 % for PSA <10, 10–20 and 20 ng/mL, respectively.

Subsequently, we investigated the relationship between biochemical control rate and ADT duration. The 5-year biochemical control rates were 84 and 94 % for ≤12 months and >12 months of ADT, respectively. No significant difference was observed between the two groups.

The incidence of late complications was evaluated using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). No grade 4 late genitourinary complications were observed. Grade 3 late genitourinary complications occurred in 2 patients (4 %; urinary retention and incontinence). Grade 2 late genitourinary complications occurred in 5 patients (10 %). Grade 3 late gastrointestinal complications (rectal bleeding healed by hyperbaric oxygen therapy) were observed in 1 patient (2 %). Grade 2 late gastrointestinal complications (rectal bleeding) occurred in 1 patient (2 %).

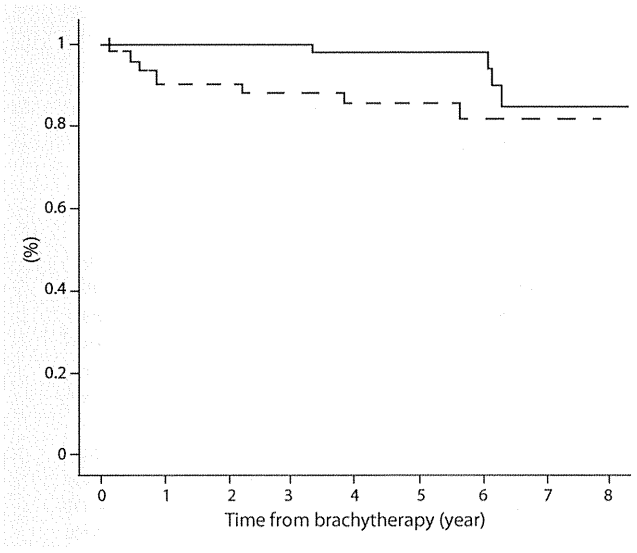

Fig. 1 ◀ The overall survival and biochemical control rates are shown (overall survival rate *solid line*; biochemical control rate *dashed line*)

Discussion

The number of reports of HDR-ISBT monotherapy eliciting good treatment results has increased recently [1, 3, 5–7, 9, 13, 14, 17, 19, 27, 32]. HDR-ISBT as monotherapy has been used to treat low- and intermediate-risk patients [1, 3, 5, 6, 9, 13, 14, 17, 19]; however, several groups have also reported its effectiveness in high-risk patients [7, 27, 32] (◘ **Table 2**). For example, Hoskin et al. [7] analyzed 197 patients using MRI and the NCCN classification for staging workup; these authors reported that the 3-year biochemical control rate was 91% for high-risk patients. In particular, Zamboglou et al. [32] evaluated >700 patients treated with HDR-ISBT as monotherapy using dose fractionation schedules of 34.5–38 Gy in 3–4 fractions; these authors reported a 5-year biochemical control rate of 93% for high-risk patients.

In contrast, Krauss [11] commented that there were two points of caution in the report by Zamboglou et al. [32]: Krauss pointed out that the staging workup (via MRI) and risk group definition led to the superior outcomes observed in the subset of high-risk patients of the latter publication. The prognostic value of MRI-staged disease is not clearly defined. Furthermore, they used risk classification criteria identifying high-risk as ≥ T2c. According to the NCCN criteria, T2c is considered intermediate risk. If these criteria are used, several patients classified as high-risk would have been reclassified as intermediate-risk.

Krauss [11] suggested the over-evaluation of HDR-ISBT as monotherapy for high-risk patients by patient risk-group migration. However, this factor seems to have a minor influence on the significance of the study. For example, we previously reported our results of a multi-institutional retrospective analysis of conventional 60–70 Gy EBRT for prostate cancer [31], which included 436 patients treated between 1999 and 2006. In this study, MRI was included in the staging workup for almost all patients. In the same study, the 5-year progression-free survival rates were 69 and 67% for high-risk and very-high-risk patients, respectively, using the NCCN classification criteria. In contrast, the European Groupe d'Etude des Tumeurs Uro-Génitales (GETUG)-01 trial performed during the same period in Europe [16] evaluated 444 patients who were treated with an irradiation dose of 66–70 Gy between 1998 and 2004. However, in the GETUG-01 trial, MRI was not included in the staging workup. In the high-risk group (T3 and/or Gleason score≥7 and/or PSA ≥3× the upper normal limit), the 5-year progression-free survival rates were 63 and 60% for EBRT to the prostate alone and to the pelvis plus prostate, respectively, which were similar to the results reported in this study. On the basis of these results, we reasoned that the influence of MRI for staging workup does not have a significant impact.

In this study, we evaluated biochemical control results and showed a rate of 87% among 48 high-risk patients, including 9 very-high-risk patients. Because this result was lower than that reported by Zamboglou et al. [11], patient risk-group migration may explain such differences. However, we considered the difference to be a relatively minor problem; although it may not be negligible in all cases. From these arguments, we believe that the treatment results reported by Zamboglou et al. remain valuable.

Pelvic nodal irradiation should be considered in cases where HDR-ISBT as monotherapy is an option in high-risk patients. Roach et al. [18] reported that pelvic nodal irradiation was effective for patients with a 15% risk of lymph node involvement. However, opposing opinions have also been reported [8, 21]. Although EBRT is administered to the pelvis, it often results in unsatisfactory outcomes if the total prostate doses are insufficient (total dose 66–70 Gy). Compared with the results of HDR-ISBT as monotherapy [16], the results of conventional EBRT to the pelvis plus prostate in the GETUG-01 trial appear poor, as the 5-year progression free survival rate was only 60% (◘ **Table 2**). The Radiation Therapy Oncology Group(RTOG) 94-13 trial demonstrated similar results [12]; here, the 5-year biochemical control rate was approximately 70% (estimated from figure) for conventional EBRT to the pelvis plus prostate with both adjuvant and neoadjuvant ADT arms. Challapalli et al. [2] reviewed the treatment results of a series that combined EBRT and HDR-ISBT and reported that the 4–10 year biochemical control rate was 62–97% for high-risk patients. These reports showed that HDR-ISBT as monotherapy elicited better treatment results than conventional EBRT to the pelvis plus prostate; they also showed that its efficacy was almost equivalent to that of combined HDR-ISBT and EBRT—even among high-risk patients.

With regard to toxicity profiles, HDR-ISBT as monotherapy showed outcomes equivocal to other treatments. For example, Zamboglou et al. [32] reported that the rate of late grade ≥3 genitourinary complications was 2–7% for three types of dose fractionation schedules

Table 2 Biochemical control rate after high-dose-rate interstitial brachytherapy as monotherapy

Authors; reference	No. patients	Dose per fraction (Gy)	Total dose (Gy)	Risk classification	MRI for staging workup	ADT for each risk class (%)	Risk class (no. patients)	Biochemical control rate (%)
Yoshioka et al. [27]	112	6	54	Modified NCCN[a]	Yes	60	Low (15)	85
–	–	–	–	–	–	66	Intermediate (29)	93
–	–	–	–	–	–	97	High (68)	79
								At 5 years
Zamboglou et al. [32]	718	9.5	38	Zamboglou's criteia[b]	Yes	16	Low (395)	95
–	–	9.5	38	–	–	27	Intermediate (177)	93
–	–	11.5	34.5	–	–	56	High (146)	93
								At 5 years
Hoskin et al. [7]	197	8.5	34	Modified NCCN[a]	Yes	50	Low (8)	95
–	–	9	36	–	–	74	Intermediate (103)	99
–	–	10.5	31.5	–	–	92	High (86)	91
–	–	13	26					At 3 years
This study	48	9.5	38	Modified NCCN[#]	Yes	100	High (48)	87
–	–	6	54	–	–	–	–	At 5 years
–	–	7	49	–	–	–	–	–

[a]National Comprehensive Cancer Network (NCCN) guidelines. The classification was modified and very-high-risk patients were included into the high-risk patients group
[b]Low risk was tumor stage T1c–T2a, with a prostate-specific antigen (PSA) level < 10 ng/mL and Gleason score ≤ 6; intermediate risk was T2b, PSA 11–20, ng/mL or Gleason score 7; high risk was ≥ T2c, PSA > 20 ng/mL or Gleason score > 7 or two intermediate-risk criteria
ADT androgen deprivation therapy

Table 3 Genitourinary and gastrointestinal late complications (grade ≥ 3) after high-dose-rate interstitial brachytherapy as monotherapy

Authors; reference	No. patients	Grading system	Grade ≥ 3 late complication	
			Genitourinary (%)	Gastrointestinal (%)
Yoshioka et al. [27]	112	CTCAE v.3.0	3	2
Zamboglou et al. [32]	718	CTCAE v.3.0	2–7	0.4–4.2
Hoskin et al. [7]	197	RTOG	3–16	0–1
This study	48	CTCAE v.3.0	4	2

CTCAE v.3.0 Common Terminology Criteria for Adverse Events version 3.0, RTOG, Radiation Therapy Oncology Group

(**Table 3**). The present study showed comparable results (4%). Furthermore, Hoskin et al. [7] reported that the rate of late grade ≥ 3 gastrointestinal complications was 0–1%; whereas Zamboglou et al. reported that this was 0.4–4.2%. Similarly, one (2%) grade 3 gastrointestinal complication was observed in the present study (**Table 3**). Challapalli et al. [2] reviewed the late complication rates of combined EBRT and HDR-ISBT, and showed that the median grade ≥ 3 genitourinary toxicity rate was 4.5% (range 0–14.4%) and the median grade ≥ 3 gastrointestinal toxicity rate was 0.5% (range 0–4.1%). These reports showed that HDR-ISBT as monotherapy showed results similar to those of combined HDR-ISBT and EBRT.

Conclusion

Our results showed that HDR-ISBT combined with ADT demonstrates promising biochemical control, even in high-risk patients. In addition, the results showed that the late genitourinary and gastrointestinal complication rates were acceptable.

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Compliance with ethical guidelines

Conflict of interest. K. Yoshida, H. Yamazaki, T. Takenaka, T. Kotsuma, M. Yoshida, K. Masui, Y. Yoshioka, Y. Narumi, T. Oka and E. Tanaka state that there are no conflicts of interest.

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Original paper

High-dose-rate interstitial brachytherapy for mobile tongue cancer: preliminary results of a dose reduction trial

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Abstract

Purpose: To compare the outcome of our facility with another about the shortened schedule (60 Gy in 10 fractions to 54 Gy in 9 fractions) of high-dose-rate interstitial brachytherapy (HDR ISBT) for mobile tongue cancer.

Material and methods: Eighteen patients were treated with HDR ISBT as a monotherapy in dose reduction schedule with some unique technique to determine the border of tumor accuracy (lugol's staining and metal marker), and to minimize adverse effect (lead-lined silicon block) at our facility.

Results: The 2-year local and regional control rates and cause-specific survival rate were 82%, 80%, and 83% and moderate to severe late complications occurred in five patients (28%), which were almost the same treatment results achieved by another facility.

Conclusions: We recommend 54 Gy in 9 fractions over 7 days as a feasible treatment to reduce patient discomfort in mobile tongue cancer patients.

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Key words: dose reduction, high-dose-rate brachytherapy, tongue cancer.

Purpose

Mobile tongue cancer is highly curable with radiation therapy, especially interstitial brachytherapy (ISBT). Many institutions have reported successful results using low-dose-rate (LDR) ISBT [1-5]. However, there are some shortcomings, such as radiation exposure to medical staff and no dose optimization, with this treatment. To solve these problems, some institutions adopted high-dose-rate (HDR) ISBT using a remote afterloading system. There are some advantages of HDR ISBT; for example, no radiation exposure to medical staff and better dose optimization after implantation. For HDR ISBT treatment, they implemented a dose fractionation schedule of 60 Gy in 10 fractions over approximately 8 days at a distance of 5 mm from the radioactive source and achieved good treatment results [6], which were comparable to those of LDR ISBT [6-9]. However, HDR ISBT is uncomfortable and poses a risk to patients, as maintaining applicators in the oral to submandibular region for long periods causes significant irritation and a risk of sputum aspiration. Thus, it is necessary to shorten the treatment period, even if it is by only one day. In addition, a recommended dose fractionation schedule has not yet been adopted by the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) or the American Brachytherapy Society [10,11]. Some authors investigated alternative treatment schedules conducted at Osaka University Hospital to reduce the dose amount and treatment period without compromising treatment outcomes, and determined that 54 Gy in 9 fractions showed outcomes compatible to 60 Gy in 10 fractions [12,13]. In 2001, we adopted this shortened schedule at our institution to affirm the effectiveness of this dose fractionation schedule. In this study, we present the preliminary outcome of HDR ISBT for mobile tongue cancer using the new dose reduced protocol at our institution.

Material and methods

Between February 2001 and February 2009, 18 patients with previously untreated, locally limited mobile tongue

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cancer were treated with HDR ISBT as a monotherapy at our institution. Prior to the treatment, we obtained verbal and written informed consent from all patients. All tumors were histologically identified as squamous cell carcinomas. Table 1 lists patient characteristics. The median patient age was 61 years (range 34-84 years), and median follow-up time was 49 months (range 10-121 months). Using the 2002 Union for International Cancer Control classification system, 3, 11, and 4 patients were classified as T1, T2, and T3, respectively. In regard to morphological type, 8 and 10 patients had superficial - and infiltrative - type of cancer, respectively. Implantation was performed under general anesthesia in all patients except one, who received local anesthesia because of insufficient pulmonary function. Inspection and palpation was performed by more than two physicians and Lugol's iodine staining was performed to estimate the superficial extension of the tumor [14-16]. Intraoral ultrasonography (SSD-1000®; Hitachi Aloka Medical Ltd., Tokyo, Japan) was performed to define tumor thickness [17]. Before implantation, at least four titanium seed markers were injected at the anterior, posterior, lateral, and medial edges of the lesion to plan the treatment (Fig. 1) [18]. Two or three planes were adopted for implantation with a custom - made vinyl template for guidance. We selected two planes for implantation if the thickness of the tumor was ≤ 10 mm, and three planes for implantation if the thickness was > 10 mm. As the first step of applicator implantation, an open-ended hard metal guiding needle (Bevel point needle®; Elekta AB, Stockholm, Sweden) was inserted from the submandibular region to the mouth floor or tongue mucosa with the guidance of the custom - made vinyl template or intraoral ultrasonography. The needle exit points were determined using the custom - made vinyl template on the tongue surface. The applicators in the lateral plane penetrated the mouth floor mucosa and made direct contact with the lateral border of the tongue mucosa in almost all cases. The applicators in the medial plane were implanted into the edge of tumor lesion. After implantation of the guiding needle, the flexible applicator was replaced. These applicators were then fixed with a button in the submandibular region following removal of the guide needle. Two types of flexible applicators were used: one was a linearly implanted Single-leader applicator® (Elekta AB, Stockholm, Sweden) with a one-sided button, whereas the second was a loop Double-leader applicator® (Elekta AB, Stockholm, Sweden). The loop technique was used near the oropharyngeal region because the button of the single-leader applicator on the mucosal surface of the tongue caused irritation for patients (Fig. 1). On the basis of the lesion size, this procedure was repeated to place a sufficient number of flexible applicators. After implantation, the parallelism of the applicators was verified via intraoral ultrasonography (Hitachi Aloka Medical Ltd, Japan).

We performed two dimensional treatment plan. Two orthogonal X-ray images were captured to confirm applicator positions using dummy sources. The basal dose points were defined on central plane. For triangular arrangement of applicators, the basal dose rates were calculated at the center of gravity of each triangle. The reference isodose, where we prescribed 54 Gy in 9 fractions over 7 days, was 85% of the mean basal dose rates (Fig. 1). All treatment planning was performed using the PLATO® cancer treatment planning system (Elekta AB, Stockholm,

Table 1. Clinical characteristics of patients

	N
Age (years)	
Range	34-84
Median	61
Gender	
Male	10
Female	8
TNM classification	
T1N0M0	3
T2N0M0	11
T3N0M0	4
Tumor type	
Superficial	8
Infiltrative	10

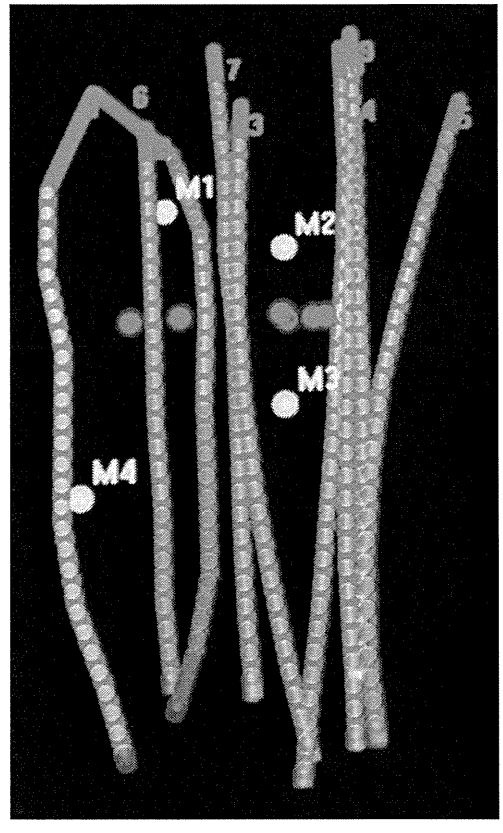

Fig. 1. Four titanium seed markers were injected into the anterior, posterior, lateral, and medial edges of the lesion to plan treatment (yellow points; M1-4). The loop technique was used between applicator number 1 and 6. The other applicators (numbers 2-5 and 7-9) were linearly implanted. Basal dose points and source dwell points are indicated by blue and red points, respectively

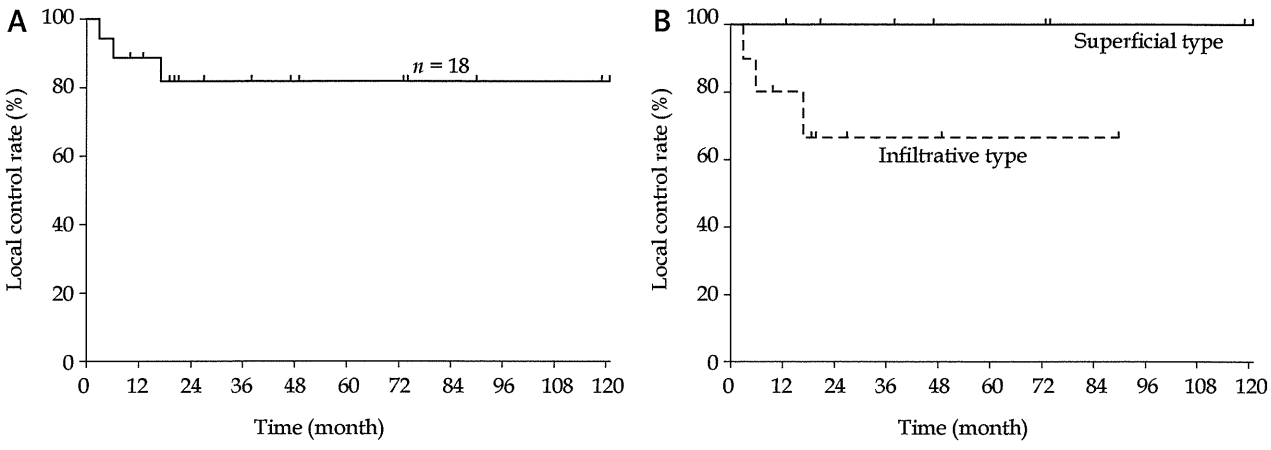

Fig. 2. Local control rate (A) and morphological type (B) in mobile tongue cancer following HDR ISBT

Sweden) with manual modifications [18]. Initially, we used computer optimization (geometrical optimization) then manually modified the dwelling times to deliver prescribed dose to titanium seed markers.

We used a lead block covered with siliconized rubber as a spacer to separate the gingival mucosa and mandible from the radioactive source. Only the silicone block was used to prevent metal artifacts at the time of CT for treatment planning. Two fractions were administered each day, and the time interval between fractions was > 6 h. We used the microSelectron-HDR® brachytherapy applicator (Elekta AB, Stockholm, Sweden) as the ^{192}Ir radioactive source. Local and regional control rates, cause-specific survival (CSS) rates, and complications were analyzed. Survival curves were constructed using the Kaplan-Meier method.

Results

Of all 18 patients, three T2 cases experienced local recurrence: the first occurred at 3 months after treatment, the second at 6 months, and the third at 17 months. Recurrence in one patient happened because of over – insertion of the siliconized rubber – coated lead block. Two of the three patients underwent salvage surgery, and have maintained local control at the time of this report. There were no recurrences 2 years after treatment. The 2-year local control rate was 82%, whereas the 2-year local control rates were 100%, 72%, and 100% for T1, T2, and T3 cases, respectively. The 2-year control rates were 100%, and 67% for the superficial and infiltrative morphological types, respectively (Fig. 2). The overall neck metastasis occurred in 10 patients. Nine of 10 patients (90%) had a lymph node metastasis within 2 years. One patient experienced lymph node metastasis at 34 months after treatment. Of all patients with nodal metastasis, they were treated with radical neck dissection (RND). Two of the 10 patients treated with RND died of nodal metastasis, and 2 with intercurrent disease. Ultimately, nodal metastasis were controlled in 8 of 10 patients (80%). For T1, T2, and T3 patients, the neck metastases were occurred in 1 (33%), 6 (55%), and 2 (50%) patients within 2 years after HDR ISBT. In early (T1T2N0) and advanced (T3N0) stages, seven (50%) and 2 (50%) patients had a lymph node metastasis, and for the superficial and infiltrative morphological types, two (25%) and seven (70%) patients had a nodal metastasis within 2 years after HDR ISBT, respectively. The 2-year CSS rates was 83%. The 2-year CSS rates were 67%, 90%, and 75% for T1, T2, and T3 cases, respectively. In early (T1T2N0) and advanced (T3N0) stages, the 2-year CSS rates were 85%, and 75%, respectively. The 2-year CSS rates were 88%, and 79% for the superficial and infiltrative morphological types, respectively.

Concerning adverse effects, such as one severe acute complication of sputum aspiration, which occurred during the treatment period, was transiently managed using a respirator. Moderate to severe late complications occurred in five patients (28%) who developed soft tissue necrosis or mandibular complications. One of these five patients received partial sequestrectomy, and all other symptoms were improved via drug and/or hyperbaric oxygen therapy.

Discussion

To overcome the deficiencies of LDR ISBT for mobile tongue cancer, some institutions have implemented HDR ISBT, but at the outset, lower local control rates were reported in some studies. For example, Lau *et al.* reported a local control rate of 53%, using 45.5 Gy in 7 fractions [19]. However, we consider that their dose was insufficient to accomplish a radical curative effect for mobile tongue cancer. In contrast, another institution carried out a Phase I/II study of HDR ISBT for head and neck cancer, and chose a total dose of 60 Gy in 10 fractions over approximately 8 days as a standard schedule for radical HDR ISBT of head and neck cancer [20]. In addition, they conducted a Phase III study to compare the treatment results of HDR ISBT vs. LDR ISBT for mobile tongue cancer. The preliminary and far longer follow-up results of these studies were previously reported (87% and 88% for 5-year local control and CSS rates, respectively) [6,7,21]. In addition, they performed further studies to evaluate their previous results [8,9], and found that the results of HDR ISBT were the same as LDR ISBT. Thus, they concluded that HDR ISBT is a suitable alternative to LDR ISBT for mobile tongue cancer.

However, we considered that an adequate dose fractionation schedule has not yet been reached. In a previous dose reduction study at Osaka University Hospital, Okamoto *et al.* [12] reported 3-year local control rates of 90% and 89.4% with a total dose of 60 Gy and < 60 Gy, respectively, whereas Akiyama *et al.* [13] reported 2- and 3-year local control rates of 88% using both 54 Gy and 60 Gy, respectively. Nevertheless, further studies are needed to evaluate these results. The aim of this study was to confirm the outcome with the shortened schedule of 54 Gy in 9 fractions over 7 days at our institution. Inoue *et al.* [6,7] reported that 2-year local control rates of T1T2N0 was 100%, whereas the results in our study of 2-year local control rates, including T1T2N0 cases, was 77%, which were slightly lower than those previously reported. Local control for advanced stage cases was satisfactory. Kakimoto *et al.* [8] reported that the 2-year local control rate for T3N0-2 was 71%, whereas that of our study was 100%. The 2-year control rates were 100% and 67% for the superficial and infiltrative morphological types, respectively, which were better than those reported previously [3]. Two of the three patients underwent salvage surgery and have maintained local control at the time of this report. Yamazaki *et al.* [22] reported a higher ratio of nodal involvement in infiltrative types than in superficial types and our results were consistent with this. Inoue *et al.* [6,7] reported 2-year nodal control rates for T1T2N0 of 79%. Shibuya *et al.* [3] reported that T1T2N0 patients having superficial - type tumors had a lower incidence of a metastasis (30%) compared with those having infiltrative - type tumors (54%). The result of our study showed fifty percent of patients in T1T2N0 cases had a nodal failure, which was slightly higher than those previously reported. Some authors reported that locoregional control rates in the management of early or superficial mobile tongue cancer were higher in the group treated with brachytherapy alone than in that of external irradiation combined with brachytherapy [23-25]. Therefore, we treated our patients with brachytherapy alone. However, our results of nodal failure were worse, because we believe, a larger number of our patients had a infiltrative - type of tumors. In 2009, GEC-ESTRO reported that brachytherapy alone is recommended for T1N0 and T2N0 tumor that are smaller than 4 cm. For tumors > 3-4 cm or N1 lesions, brachytherapy can be delivered as a boost after 40-45 Gy of external beam irradiation to the neck and oral cavity [10]. Because of this, primary HDR ISBT as monotherapy for the management of patients with mobile tongue cancer might be an option only in selected cases (for example, T1T2N0, superficial tumors). In case of large and infiltrating tumors, external beam irradiation should be added to avoid unacceptably high rate of nodal failure. Of all patients with nodal metastasis, they were treated with RND. Ultimately, 80% of patients with nodal metastasis were controlled. Thus, we consider that our results were, to some degree, valid.

In the present study, the 2-year CSS rate was 85%. Kakimoto *et al.* [8] reported 2 - CSS rates of 57% in T3N0-2 patients, whereas in our study, the 2-year CSS rate was 75% in T3N0 patients. Thus, we consider that our results were almost similar to those in previous reports.

Inoue *et al.* [7] and Yamazaki *et al.* [9] reported that the incidence of complications were 12% and 10%, respectively. In the present study, the complication rate was 28%; however, the conditions of four patients improved via drug and/or hyperbaric oxygen therapy.

To improve treatment results, we implemented several unique techniques. For example, we applied Lugol's iodine staining [14-16] and titanium seed marker implantation [18] to estimate the extension of the tumor (Fig. 1). In future trials, to decrease the incidence of complications, we will deliver adequate doses to cover the clinical target volume (CTV) without exposing the tongue mucosa and mandible to excessive radiation using this 3 dimensional (3D) image-based treatment planning system. Recently, gynecological planning for HDR ISBT is shifting to 3D image-based planning using computed tomography and magnetic resonance imaging [26]. However, few studies have been reported regarding 3D image-based techniques for head and neck cancer [27,28]. We will gradually implement 3D image-based HDR ISBT for mobile tongue cancer using this method at our institution, and we believe that we will achieve better treatment results and reduce complications and patient discomfort.

Conclusions

In conclusion, we found that a dose reduction to 54 Gy in 9 fractions over 7 days in HDR ISBT for mobile tongue cancer is feasible, especially for T1T2N0, superficial tumors, for reducing patient discomfort, which strongly supports preceding study.

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Disclosure

Authors report no conflict of interest.

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