Table 1. Results of HDR brachytherapy for oral tongue cancer

Author (year) Institute	¶*n*	T category	§Schedule	†Local control	Toxicity	Remark
Lau (1996) [7] British Columbia Cancer Agency, Canada	27	10T1, 15T2, 2T3	Bx only: 6.5 Gy × 7 fr	53% 5/10 T1, 7/15 T2, 2/2 T3	37% toxicity	HDR; lower local control rate higher severe complication rate
Leung (1997) [8] Tuen Mun HP, Hong Kong	8	5T1, 3T2	Bx only: 6 Gy × 10 fr	100%	1G3 both S + B	HDR feasible
Leung (2002) [9] Tuen Mun HP, Hong Kong	19	10T1, 9T2	Bx only: 5.5 Gy × 10 fr	94% (4 y)	1G2 both S + B	HDR feasible
Ohga (2003) [10] Fukuoka, Japan	28	8T1, 15T2, 5T3	Bleomycin + EBRT: 40–6 5 Gy + Bx: 4–5 Gy × 2–4	96% (2 y)	late 18% S15%, B4%	chemoradiotherapy Bleomycin reduce Bx dose
Umeda (2005) [11] Kobe, Japan	26 HDR	8T1, 18T2	Bx only: 6 Gy × 9–10	65%	NA	surgery optimal Tx
	78 LDR	42T1, 36T2	Bx only: 61 Gy (Ra–226, Cs–137)	83%		
	71 surgery	42T1, 29T2		94%		
Nishioka (2006) [12] Sapporo, Japan	4	1T3, 3T4	Ia CDDP: 100–120 mg + EBRT: 30 Gy + Bx: 6 Gy × 7 (5–8)	LRC 100%	100% G3 mucositis	intraarterial chemoradiotherapy ia can reduce Bx dose
Patra (2009) [13] Kolkata, India	33	advanced 18, early 15	EBRT: 50 Gy (46–66 Gy) + Bx: 3–3.5 Gy × 4–7 (14–21 Gy)	79% CR + 21% PR 100% early, 78% advanced disease**	12% G3 mucositis and other***	
Guinot (2010) [14] Valencia, Spain	50	42T1–2, 8T3	33PT EBRT: 50 Gy + Bx: 3 Gy × 6 (12–24.5 Gy)	94% T1, 84% T2, 0% T3	16% S, 4% B	3–4 Gy/fr feasible
		16N +	17PT Bx only: 4 Gy × 11 (42–49 Gy)	Bx 100% vs EBRT + Bx 69% ($P = 0.04$)		
Osaka University						
Teshima (1992) [18] Phase I/II dose escalation trial	7 various (4 tongue)	T1–3N0	EBRT: (32–52 Gy) + Bx: 3.5 Gy × 10 ⇒ 6 Gy × 10	100% CR	no early complication	HDR 6 Gy × 10 feasible
Inoue Ta (2001) [21] Phase III randomized trial	25 HDR	14T1, 11T2	Bx only: 6 Gy × 10	87%	15% toxicity	HDR ≃ LDR prospective study
	26 LDR	14T1, 12T2	Bx only: 70 Gy/4 9 days	84%	HDR B2, Both arms S1	T1–2N0 HDR vs LDR

Continued

Table 1. *Continued*

Author (year) Institute	¶*n*	T category	§Schedule	†Local control	Toxicity	Remark
Yamazaki (2003) [22] T1–2N0 Bx only	58 HDR	22T1, 36T2	Bx only: 6 Gy × 8–10	84%	S2%, B2%, both 1%	HDR ≃ LDR in T1–2
	341 LDR*	171T1, 170T2	Bx only: 70 Gy (6–84 Gy)	80%	S3%, B3%, both 1%	
Yamazaki (2007) [23] T1–2N0	80 HDR	24T1, 47T2, 9T3	EBRT: 37 Gy ± Bx: 6 Gy × 6–10	87%T1, 79%T2, 89%T3	Bx 19%, Bx + EBRT 29%	HDR ≃ LDR in T1–3
	217 Ra–226	77T1, 103T2, 37T3	EBRT: 29 Gy ± Bx: 72 Gy (59–94 Gy)	85%, 75%, 62%	Bx 9% Bx + EBRT 24%	EBRT elevated toxicity
	351 Ir–192	111T1, 202T2, 38T3	EBRT: 30 Gy ± Bx: 72 Gy (59–94 Gy)	79%, 73%, 64%	Bx 10%, Bx + EBRT 28%	
Kakimoto (2001) [24] T3N0–2	14 HDR	All T3	EBRT: 30 Gy (12.5 – 60 Gy) ± Bx: 6 Gy × 10	71% (2 y)	S21% B0%	HDR ≃ LDR in T3
	61 LDR Ir–192		EBRT: 30 Gy (12.5–60 Gy) ± Bx: 72 Gy (5 –94 Gy)	67% (2 y)	S5% B20%	
Akiyama (2012) [25] T1–2N0 60 Gy vs 54 Gy	17 54 Gy arm	7T1, 10T2	Bx only: 6 Gy × 10	88% (2 y)	S0%, B6%, both 12%	6 Gy × 9 ≃ 6 Gy × 10
	34 60 Gy arm	16T1, 18T2	Bx only: 6 Gy × 9	88% (2 y)	S3%, B3%, both 6%	

n = number of patients, EBRT = external beam radiotherapy, Bx = brachytherapy, B = bone exposure and/or necrosis (late complication), S = ulcer soft tissue (late complication), ia = intraarterial infusion, CR = complete response, PR = partial response, LRC = locoregional control, NA = not available, CRT = chemoradiotherapy, G = grade, *227Ir-192:113 Ra-226:1both, **including surgical salvage, ***9% transient hemorrhage (3% local infection, 3% severe dysphasia, 15% xerostomia Grade 3-4), ¶HDR unless otherwise stated, §twice a day unless otherwise stated, †5 y unless otherwise stated.

Umeda *et al.* reported the results of a retrospective study comparing the efficacy of LDR-ISBT, HDR-ISBT, and surgery for early tongue cancer [11]. In total, 180 patients with Stage I/II tongue cancer were divided into three treatment groups: LDR ($n=78$), HDR ($n=26$) and surgery ($n=71$). Local recurrence was seen in 13 patients (17%) in the LDR group, 9 (35%) in the HDR group, and 4 (6%) in the surgery group. After salvage therapy, a final local cure was achieved in 71 patients (91%) in the LDR group, 22 (85%) in the HDR group, and 71 (100%) in the surgery group. The respective 5-year overall survival rates for the LDR, HDR and surgery groups were 84.0%, 72.9% and 95.4% for patients with Stage I tumors and 72.2%, 51.5% and 93.8% for patients with Stage II tumors, respectively. Umeda *et al.* [11] concluded that surgery is the optimal treatment method for patients with Stage I/II tongue cancer. However, a substantial treatment bias was present in that study because of its retrospective nature.

Nishioka evaluated the efficacy and safety of intraarterial cisplatin infusion plus EBRT and HDR brachytherapy [12]. Superselective intraarterial infusion of cisplatin (100–120 mg) was performed concomitantly with EBRT in four patients with locally advanced carcinoma of the tongue. All patients received an HDR-ISBT boost after combination therapy. Brachytherapy was performed twice daily after EBRT with a fraction of 6 Gy up to a total of 30–48 Gy. All patients completed the therapy as scheduled. No vascular or neurological complications were observed. Grade 3 acute radiation mucositis developed in all patients, but this did not necessitate a treatment break. After a mean follow-up period of 35 months, locoregional control had been achieved for all patients.

Patra *et al.* treated 33 patients with oropharynx and oral cavity carcinomas with HDR-ISBT after EBRT at Medical College Hospital, Kolkata [13]. Early stage disease (Stage I/II) was noted in 15 patients, and advanced stage disease (Stage III/IV) was diagnosed in 18. All received EBRT at a median dose of 50 Gy (range, 46–66 Gy) to the primary tumor and regional lymph nodes before brachytherapy. Node-positive patients with residual neck disease also underwent neck dissection. The brachytherapy dose in combination with EBRT ranged from 14–21 Gy (3–3.5 Gy per fraction, two fractions daily). The follow-up period was between 18 and 40 months. At the end of radiation treatment, complete response was achieved in 79% of patients, and partial response was achieved in 21%. The ultimate control rates (including surgical salvage) were 100% and 78% for early and advanced disease, respectively. Local failure occurred in three patients (9%) after complete response. No distant metastasis was observed during follow-up. Grade 3 mucositis was observed in 12% of cases. Transient hemorrhage occurred in three (9%) patients and local infection in one (3%) patient. Severe dysphagia developed in one (3%) patient. Severe xerostomia (Grade 3/4) occurred in five of 33 (15%) patients; most patients experienced less severe xerostomia (Grade 1/2).

Guinot *et al.* reported on 50 patients treated for oral cavity carcinoma with HDR-ISBT [14], 42 of whom were diagnosed as having Stage T1/2 tumors and 8 of whom had Stage T3 tumors. In addition, minimal lymph node involvement (Stage N1) was confirmed in 16 patients, but no lymph node involvement was observed in the other 34 patients (N0 stage). ISBT alone was administered to 17 (T1/2N0) patients (34%), and 33 patients (66%) received ISBT complementary to EBRT. A perioperative technique was performed for 14 patients. The median total radiation dose was 44 Gy when HDR brachytherapy was used alone (4 Gy/fraction), and 18 Gy was used when HDR brachytherapy was complementary to 50 Gy EBRT (3 Gy/fraction). Actual disease-free survival rates at three and five years were 81% and 74%, respectively (median follow-up, 44 months). Local failure developed in 7 patients. Local control rates at three and five years, respectively, were as follows: 87% and 79% (T1/2); 94.5% and 91% (T3); and 43% and 43% (with salvage surgery). Local control was maintained in all the cases in which HDR brachytherapy was the sole treatment. Local control rates in the combined treatment group (EBRT + HDR-ISBT) were 80% and 69% at three and five years, respectively ($P=0.044$). Soft tissue necrosis developed in 16%, and bone necrosis developed in 4% of the cases. Guinot *et al.* [14] concluded that HDR brachytherapy is an effective method for the treatment of tongue carcinoma in low-risk cases. Doses per fraction of 3–4 Gy yielded local control, and complication rates were similar to those observed in LDR brachytherapy. Results using the perioperative technique are also encouraging.

Osaka experiences

Phase I/II study: early mucosal reaction and late tongue atrophy

At Osaka University Hospital, more than 1450 patients with mobile tongue cancer were registered over the course of 30 years (Table 1) [15]. In the early years of treatment, Cobalt-60 needles were used for ISBT; however, in 1968, these were replaced by Ra-226 needles, which were used until 1987. In 1973, the first Ir-192 wire was installed in the delivery system, and manual after-loading with a guide gutter technique began. Ir-192 hairpins or Cs-137 needles are now usually used for LDR interstitial radiotherapy in Japan.

In 1991, Inoue *et al.* installed an HDR remote-controlled after-loading system using an Ir-192 microsource, the MicroSelectron-HDR (Nucletron, Veenendaal, The Netherlands) [16]. They initiated a Phase I/II study for head and neck cancer to determine the optimal schedule for multifractionated HDR brachytherapy because of the lack of a standard treatment schedule [2, 16]. Initially, a dose rate conversion factor of approximately 0.54–0.6 from LDR to HDR was

adopted, based on the results of the previous studies [6] of cervical cancer [17]. An overall treatment time of one week was established, which is the same as that of LDR brachytherapy. The dose was increased at 20% intervals starting at 35 Gy up to 60 Gy (Table 2), using the standard of 2 fractions per day with a minimum gap of 6 h because of its suitability for routine practice [18].

In Case No. 1, a dose schedule of 35 Gy/10 fractions per week was selected. A dose equivalent to 50–60 Gy of LDR interstitial radiotherapy was used for HDR brachytherapy, in this case after the administration of 52 Gy of EBRT. However, the acute mucosal reaction was milder than expected. In Case No. 2, a dose equivalent to 70 Gy of LDR interstitial radiotherapy was necessary after 30 Gy of EBRT; therefore, a dose schedule of 42 Gy/10 fractions per week was selected. However, the acute mucosal reaction was again milder than expected. In Case No. 3, the dose of HDR was increased to 50 Gy/10 fractions per week after EBRT (50 Gy) because of tumor size. Case No. 4 received no previous treatment. Therefore, a dose schedule of 60 Gy/10 fractions per week was selected [16].

No early adverse reaction related to HDR brachytherapy was observed in any of these cases. A dose schedule ranging from 35 Gy with EBRT to 60 Gy without EBRT was therefore deemed safe in terms of early mucosal reaction. Three of the four patients were alive, with no evidence of disease more than seven years after treatment. No spacer could be inserted because of the posterior location of the tumor in one patient, in whom bone exposure healed spontaneously. Of the two patients who developed soft tissue ulcers, one had previously received mantle field irradiation of 40 Gy for Hodgkin's disease. Inoue *et al.* [16] concluded that HDR brachytherapy at a dose of 60 Gy in 10 fractions over one week had the same effects as LDR of 70 Gy over one week for mobile tongue cancer.

Fading of mucosal reaction and late tongue atrophy

The EORTC/RTOG score for mucosal reaction after HDR-ISBT was almost identical to that produced by LDR brachytherapy. The development and course of mucositis were slightly faster for HDR than for LDR, although the time to peak reaction was similar (10 days after treatment). To compare LDR and HDR brachytherapy objectively, a new scoring system for mucositis was introduced. Assessment of the degree of mucosal reaction in the fading phase can be difficult using the EORTC/RTOG scoring system for intraoral mucosal reactions. Therefore, the EORTC/RTOG scoring system was modified, and the LENT-SOMA tables were developed. In a study comparing mucosal reactions between brachytherapy treatments, Sasaki *et al.* reported that the slopes of developing and fading mucosal reactions were almost the same in the LDR and HDR groups [19]. Spotted mucositis appeared 3 days after HDR hyperfractionated ISBT. Confluent mucositis developed and peaked about 10 days after treatment, but resolved after 4–8 weeks (Fig. 1) [18, 19].

In addition, to evaluate tongue hemiatrophy as a late effect of brachytherapy, Yoshioka *et al.* established a new grading system for patients who had received LDR or HDR brachytherapy for early tongue cancer [20]. In that study, 49 patients who had received brachytherapy for early tongue cancer (T1/T2, 22:27) were investigated. All patients had undergone either LDR or HDR brachytherapy with Ir-192 (LDR/HDR, 30:19) between 1980 and 1998. Atrophic changes in the tongue were classified into four categories (G0–G3) as follows: unable to protrude the tongue beyond

Table 2. Phase I/II study for oral cancer

Case No.	Age	Sex	Site	T	EBRT		Bx		BED10	BED3	Results		Adverse effect
					Gy	Frx	Gy	Frx			Status	Follow-up (months)	
1	65	M	floor	4	52	23	35	10	91	98	DT	17	(–)
2	84	M	lip	2	30	15	42	10	80	90	DID	29	(–)
3	72	M	tongue	2	50	25	50	10	113	130	DN	44	erosion
4	82	M	buccal	3	51	21	50	10	116	163	DT	10	(–)
5	40	M	tongue	1			60	10	80	108	NED	65	(–)
6	65	M	tongue	2			60	10	80	108	NED	91	bone exposure#
7	68	M	tongue	2			60	10	80	108	NED	91	ulcer*
8	73	M	tongue	3	48	24	60	10	128	156	DN	7	ulcer
9	58	F	tongue	2			60	10	80	108	NED	91	(–)

From [16] and [18]. EBRT = external beam radiotherapy, Bx = brachytherapy, DT = death from primary tumor, DN = death from lymph node, DID = death from intercurrent disease, NED = no evidence of disease, #without spacer, *prior radiotherapy for Hodgkin's Disease

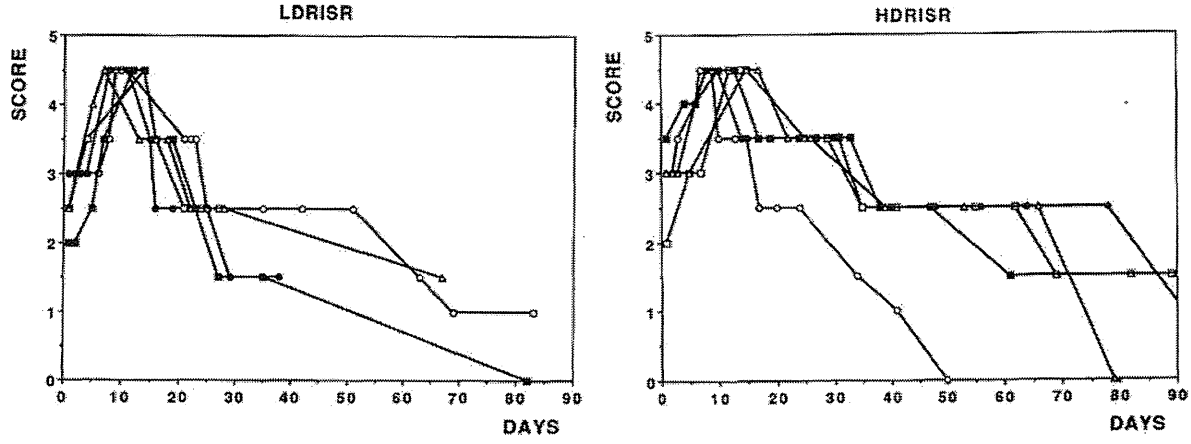

Fig. 1. Time course of mucosal reactions as observed after LDR or HDR interstitial brachytherapy for mobile tongue cancer [19].

the incisors (G3, $n=1$); hemiatrophy of the tongue on the irradiated side in the resting position (G2, $n=5$); deviation of the tip of the tongue to the irradiated side when protruded (G1, $n=29$); and none of these signs (G0, $n=14$). The relationships between tongue hemiatrophy and tumor factors, treatment factors, and functional impairment were then investigated. The median time from treatment to assessment was 75 months (range, 8–219 months). No speech or swallowing dysfunction, pain or contracted feeling, or general dissatisfaction with post-treatment tongue status was observed in G0 patients. There was a tendency for such problems to increase with higher grades of tongue hemiatrophy. The frequency of T2 and non-superficial type tumors also tended to increase with increased tongue hemiatrophy grade. The volume index of the G2 and G3 groups was significantly larger than that of the G0 and G1 groups ($P=0.041$). No significant difference in atrophic change was observed between LDR-ISBT and HDR-ISBT treatments.

Phase III study comparing outcomes of HDR and LDR brachytherapy

Inoue *et al.* conducted a prospective Phase III study comparing outcomes of HDR and LDR brachytherapy for early oral tongue cancer [21] The criteria for patient selection were as follows: (i) presence of a T1/T2N0 tumor treatable via single plane implantation; (ii) tumor localization at the lateral border of the tongue; (iii) tumor thickness ≤10 mm; (iv) performance status 0–3; and (v) absence of severe concurrent disease. In that study, which was undertaken from April 1992–October 1996, 26 patients were treated with LDR interstitial radiotherapy (ISBT: 70 Gy/4–9 days) and 25 patients with HDR-ISBT (60 Gy/10 fractions/1 week). The 5-year local control rates in the LDR and HDR groups were 84% and 87%, respectively (Fig. 2). Nodal metastasis occurred in 6 patients in each group. The 5-year nodal control rates in the LDR and HDR groups were 77% and

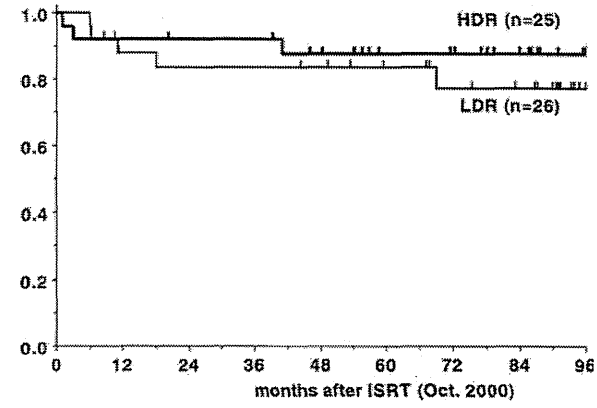

Fig. 2. Comparison of local control between HDR and LDR in Phase III study [21].

76%, respectively. Inoue *et al.* [21] concluded that local control rates in hyperfractionated HDR-ISBT for early mobile tongue cancer are similar to those in continuous LDR-ISBT, and that hyperfractionated HDR-ISBT is an effective alternative treatment to continuous LDR-ISBT. Concerning adverse effects, a tongue ulcer occurred in one patient in both groups. Bone exposure occurred in two patients in the HDR group. For one of these two patients, the spacer, which reduced the dose of radiation to the mandible, could not be used because the lesion extended to the posterior part of the tongue.

Retrospective reviews

Yamazaki *et al.* [22] conducted a general retrospective analysis of 648 T1–3N0 tongue cancer patients treated with brachytherapy with or without EBRT [23]. The 5-year local control rates for patients treated with Ra-226 and Ir-192

were 85% and 79% for T1, 75% and 73% for T2, and 62% and 64% for T3 tumors, respectively. For patients in the HDR group, 5-year local control rates were 87% for T1, 79% for T2, and 89% for T3. Furthermore, 5-year local control rates for patients treated solely with brachytherapy were 80% and 84% in the LDR ($n = 341$; T1:T2 = 171:170) and HDR groups ($n = 58$; T1:T2 = 22:36), respectively [22]. In a study of the role of HDR brachytherapy in T3 tumors, Kakimoto *et al.* reported 2- and 3-year local control rates of 67% in patients treated with LDR-ISBT. Local control rates after 2 and 3 years in patients treated with HDR-ISBT were 71% [24]. Thus, the local control rates for patients treated with HDR-ISBT were similar to those of patients treated with LDR-ISBT.

Dose reduction trials

Akiyama *et al.* analyzed the effect of a dose reduction in HDR brachytherapy from 60 Gy/10 fractions to 54 Gy in 9 fractions for early oral tongue cancer [25]. Some studies reported that 60 Gy/10 fractions results in a 14% increase in BED compared with 70 Gy LDR in $\alpha/\beta = 10$, and a 54% increase in late responding tissue, which is considered formidable [8, 9]. Mochizuki *et al.* found that a dose of 6.5 Gy × 7 fractions is equivalent to 60 Gy of LDR and may actually represent an underdose [26]. An equivalent dose of HDR-ISBT to 70 Gy of LDR-ISBT was calculated as 48 Gy in late reaction ($\alpha/\beta = 3.8$) and 54 Gy in acute reaction ($\alpha/\beta = 10$) cases [26].

Akiyama *et al.* conducted a matched-pair analysis of early oral tongue cancer patients (T1/2N0M0) treated at doses of 60 Gy ($n = 34$) and 54 Gy ($n = 17$) between 1996 and 2004 [25]. Local recurrence was observed in 2 patients in the 54 Gy arm and in 5 patients in the 60 Gy arm. The 2-year local control rate was 88% in both groups. The 2-year overall survival rates were 88% and 82% in the 60 Gy and 54 Gy arms, respectively. The 2-year actuarial complication-free rates were 91% and 83% in the 60 Gy and 54 Gy arms, respectively (n.s.). No significant association was found between total dose, local control rate, and late complications. Akiyama *et al.* [25] concluded that a dose of 54 Gy in 9 fractions was comparable to a dose of 60 Gy/10 fractions for early oral tongue cancer. A dose of 54 Gy/9 fractions for oral tongue cancer was used thereafter.

CTV-based dosimetry

To determine a clinical target volume (CTV)-based dose prescription for HDR brachytherapy, Yoshida *et al.* used metal markers in 47 patients (32 head and neck, and others) [27]. During treatment planning, they administered a tumoricidal dose to an isodose surface covering the marked CTV and reduced the dose to the organs at risk to a level lower than the constraints. Maximum doses were 80%, 150%, 100%, 50%, and 200% of the prescribed doses for the rectum, urethra, mandible, skin, and large vessels, respectively. These doses were compared with the doses theoretically calculated using the Paris system. If the Paris system (reference dose applied to an isodose surface of 85% of the basal dose) had been used, 16 patients would have been underdosed, and 4 patients (2 rectum + urethra, 1 urethra, and 1 large vessel) would have been overdosed.

In the study by Yoshida *et al.* [27] using the CTV-based dose prescription, the dose non-uniformity ratio was 0.31 ± 0.05, and the maximum diameter of the hyperdose sleeve was 4–49 mm (median, 7 mm). A statistically significant difference was observed between CTV-based dose prescription and the dosage using the Paris system (0.28 ± 0.08, 3–99 mm, median: 6 mm; $P < 0.002$, 0.0002). Of the 42 patients treated with doses higher than the tumoricidal dose, 2 experienced local recurrence, while 4 of 7 underdosed patients experienced local recurrence ($P < 0.0001$). The authors concluded that metal markers were useful in determining the optimal tumoricidal dose in relation to CTV, thus minimizing the dose to organs at risk.

Image-guided brachytherapy

Advances in HDR brachytherapy in the next decade will include integration of imaging [CT, magnetic resonance imaging (MRI), intraoperative ultrasonography, positron-emission tomography, and functional imaging] and optimization of dose distribution. Better tumor localization and improved normal tissue definition will help to optimize dose distribution to the tumor and reduce normal tissue exposure [28]. Dose distribution is calculated using the Treatment Planning System based on images of the implant (using dummy sources). Although imaging for the purposes of dose distribution was successfully achieved in the past using two orthogonal fields, the use of 3D imaging such as CT and/or MRI in head and neck brachytherapy to delineate the gross tumor volume (GTV) and CTV (despite some uncertainties) and the organs at risk (including the mandible) makes it possible to obtain objective data on dose volume histograms.

Yoshida *et al.* initiated MRI-aided image-based ISBT for evaluating gynecological tumors. They obtained MRI images after implantation and combined them with CT images in the process of planning brachytherapy [29]. CT images were obtained daily to adjust needle displacement as needed in another study [30]. Similar efforts are underway for lesions in the head and neck area.

HDR brachytherapy for other lesions

Donath *et al.* utilized HDR as the sole treatment in 13 patients with T1/2N0 malignancies of the lip ($n = 3$), tongue ($n = 1$), buccal mucosa ($n = 1$), floor of the mouth ($n = 1$), and other sites ($n = 6$) (Table 3) [31]. In total, 10 treatments at doses of 4.5–5 Gy each were delivered twice daily with a minimum of 5–6 h between treatments. At a

Table 3. Results of HDR brachytherapy for oral cancer except tongue cancer

Author (year), Institute	¶*n* Subsite	T category	§Schedule	†Local control	Toxicity	Remark
Interstitial brachytherapy						
Donath (1995) [31], McGill Univ, Canada	13 various 3 LP, 1 tongue, 1 BM, 1 FM, 6 other	T1–3N0	Bx only: 4.5–5 Gy × 10	92% (MFT:9M)	acute SE resolved in 6 weeks	HDR feasible
Inoue Ta (1996) [33], Osaka Univ, Japan	16 HDR FM	4T1, 11T2, 1T3	EBRT: 30–40 Gy ± Bx: 6 Gy × 6–8	94% (T1: 100%, T2:100%)	38% S + B	HDR ≃ LDR
	41 LDR Au–198 FM	22T1, 19T2	EBRT: 30–40 Gy ± Bx: 65–85 Gy	69% (T1: 85%, T2: 67%)	32% S + B	
Rudoltz (1999) [32], St Vincent's Medical Center, USA	55 various 16 oral + 39 OPC	16T1, 26T2, 8T3, 5T4	EBRT: 55.2 Gy (45–70.2 Gy)	79% (2Y)	16% toxicity (all OPC)	feasible for T1–2 tumor
			Bx: 16.8 Gy (12–30 Gy) 1.2–5 Gy/fx	87% T1–2 vs 47% T3–4, $P < 0.0.1$		more aggressive Tx required for T3–4 tumor
Guinot (2003) [34], Valencia, Spain	39 LP	21T1, 6T2, 12T4	EBRT: 40.5–45 Gy + Bx: 4.5–5.5 Gy × 8–10 fr	88% (4y) 95% T1–2, 74% T4, $P < 0.05$	like LDR	HDR ≃ LDR
Kotsuma (2012) [35], Osaka Univ, Japan	36 BM 14 HDR, 15 LDR*, 7 Mold**	3T1, 23T2, 7T3, 3T4	LDR*: EBRT + Bx: 70 Gy (42.8–110 Gy)	100% T1, 85.6% T2, 53.6% T3, 33.3% T4	2 Grade 3 LDR	HDR ≃ LDR
		12 N +	HDR: EBRT + Bx: 6 Gy × 8 fr (24–60 Gy)	80% HDR vs 65% LDR		
Mold						
Nishimura (1998) [36], Kinki Univ, Japan	8 4 BM, 2 FM, 2 GV	2T1, 6T2	EBRT: 40-60Gy + Bx: 3–4 Gy × 4–7	88% CR	no serious SE	thick/RMT tumor
				3 rec (2 RMT)		unfavorable for mold
Ariji (1999) [37], Nagasaki, Japan	4 2 FM, 1 BM, 1 GV	3T1, 1T2	EBRT: 22–40 Gy + Bx: 2.5–3 Gy × 10	100%	no SE	importance of dental technique
Obinata (2007) [38], Sapporo, Japan	2 1 OPC, 1MSC	1 OPC rec T2	EBRT: 60 Gy/24fr residual ⇒Bx: 6 Gy × 2 QD	50%	no SE	importance of dental technique
		1 OKK rec (50 Gy RT previously)	EBRT: 30 Gy/12fr + Bx: 6 Gy × 5 QD	1 RMT rec		

Continued

Table 3. *Continued*

Author (year), Institute	¶*n* Subsite	T category	§Schedule	†Local control	Toxicity	Remark
Kudoh (2010) [40], Tokushima, Japan	2	1 T2N0, 1 T4aN0	EBRT: 60 Gy⇒rec Bx: 5 Gy × 10 QD	100%	no serious SE	not only palliation, but also curative TX
	1 GV, 1 FM		EBRT: 40 Gy + Bx: 6 Gy ×10 QD			
Chatani (2011) [41], Osaka Rosai HP, Japan	9	7T1N0, 2T2N0	CRT (PEP or TXT)	8/9	no serious SE	chemoradiotherapy
	3LP, 1 tongue, 1 BM, 1 FM, 6 other	EBRT: 24–50 Gy + Bx: 3 Gy × 3–6	100% (2 y)			
Matsuzaki (2012) [42], Okayama, Japan	6	2 T1, 2 T2, 2 T3	EBRT: 30 Gy + Bx: 6Gy × 4	1 rec (T2)	NA	feasible for BM and LP
	5 BM, 1LP	1 N1				

n = number of patients, Bx = brachytherapy, EBRT = external beam radiotherapy, SE = side effects, PEP = pepleomycin, TXT = taxotere, B = bone exposure and/or necrosis (late complication), QD = once a day, bid = twice a day, MFT = median follow-up time,
OPC = oropharyngeal cancer, MSC = maxillary sinus cancer, LP = lip, BM = buccal mucosa, FM = floor of mouth, GV = gingiva, RMT = retromolar trigone, CRT = chemoradiotherapy, PEP = peplomycin, TXT = taxotere,
Rec = recurrence, NA = not available, SE = side effect, *LDR – 10 Ra–226 2 Ir–198 2 Au–198 and 1 I–125, **Mold = LDR Ir–198 and Cs–137, †5 y unless otherwise stated, ¶HDR unless otherwise stated, §bid unless otherwise stated

median follow-up time of 9 months, local failure was observed in only 1 patient.

Rudoltz *et al.* reported the results of HDR-ISBT for 55 patients with primary untreated squamous cell carcinomas of the oral cavity and/or pharynx [32] of Stages T1 ($n = 16$), T2 ($n = 26$), T3 ($n = 8$), and T4 ($n = 5$). All patients received EBRT followed by HDR-ISBT. A total of 38 patients received hyperfractionated (twice daily) EBRT followed by HDR-ISBT two or three times daily. Hyperthermia was induced and an electron boost was administered to the site(s) of positive nodes in patients with cervical adenopathy. Median follow-up time in this study was 2.7 years. HDR-ISBT was extremely well tolerated. Complications developed in only 9 patients (16%): osteoradionecrosis ($n = 4$) and soft tissue necrosis ($n = 5$). These conditions resolved with conservative medical management. No complications required surgical intervention or hospitalization. Local control rates were 87% for patients with Tl (l/16) and T2 (2/26) tumors versus 47% for T3 (5/8) and T4 tumors ($P < 0.011$). Rudoltz *et al.* [32] concluded that HDR-ISBT is feasible as a boost for patients with primary squamous cell carcinomas of the oral cavity and oropharynx. Patients with Stage T1/T2 tumors fared exceptionally well; those with more advanced tumors may require more aggressive treatment, such as higher radiation doses, surgical resection, or systemic chemotherapy.

Cancer of the floor of the mouth

Patients with cancer of the floor of mouth are treated with radiation for functional and cosmetic reasons. Inoue *et al.* evaluated treatment results of HDR- and LDR-ISBT alone, and in combination with other therapeutic modalities, for cancer of the floor of mouth [33]. From January 1980 through March 1996, 41 patients with cancer of the floor of mouth were treated with LDR-ISBT using irradiated gold (Au-198) grains, and from April 1992 through March 1996 16 patients were treated with HDR-ISBT. This study included 26 T1 tumors, 30 T2 tumors, and 1 T3 tumor. For 21 patients treated with ISBT alone, a total radiation dose of 60 Gy/10 fractions/6–7 days was used in HDR brachytherapy. In LDR brachytherapy, the dose was 85 Gy/10 fractions in 1 week. For 36 patients treated with combination therapy, a total dose of 30–40 Gy of EBRT followed by a total dose of 48 Gy/8 fractions/5–6 days of HDR-ISBT or 65 Gy in 1 week of LDR-ISBT were delivered. The 2- and 5-year local control rates of patients treated with HDR-ISBT were 94% and 94%, respectively, and the rates for patients treated with LDR-ISBT were 75% and 69%, respectively. Local control rates for patients treated with HDR brachytherapy were slightly higher than those for patients treated with Au-198 grains ($P = 0.113$). As for late complications, bone exposure or an ulcer occurred in 6 of 16 (38%) patients treated with HDR-ISBT and 13 of 41 (32%) patients treated with LDR-ISBT. Inoue

et al. [33] concluded that fractionated HDR-ISBT is a safe alternative to LDR-ISBT for cancer of the floor of the mouth.

Lip cancer

Guinot *et al.* discussed the cases of 39 patients with lip carcinoma treated with HDR-ISBT [34] at doses of 5–5.5 Gy/8–10 fractions twice daily (total dose: 40.5–45 Gy). The 3-year cause-specific survival and local control rates were 91% and 88%, respectively (95% T1–2, 74% T4, $P = 0.05$). Acute and chronic reactions were similar to those in cases treated with LDR-ISBT. The authors therefore concluded that results using HDR-ISBT are equivalent to those using LDR-ISBT.

Cancer of the buccal mucosa

Kotsuma *et al.* retrospectively reviewed data for 36 patients (25 men, 11 women) with cancer of the buccal mucosa treated with curative brachytherapy with or without EBRT [35] (Stage T1, $n = 3$; T2, $n = 23$; T3, $n = 7$; and T4, $n = 3$; Clinical Stage I, $n = 3$; II, $n = 16$; III, $n = 11$; IV, $n = 6$). Nodal metastasis was evident in 12 patients at the start of treatment. LDR-ISBT (median dose: 70 Gy, range: 42.8–110 Gy) was used in 15 cases, and HDR-ISBT (median dose: 48 Gy/8 fractions, range: 24–60 Gy) was used in 14 cases. The mold technique (median dose: 15 Gy, range: 9–74 Gy) was used in 7 cases, while 31 patients also underwent EBRT (median dose: 30 Gy, range: 24–48 Gy). The period of observation ranged from 19–242 months (median: 75.5 months). The 5-year local control and progression-free survival rates were 75.7% (100% for T1, 85.6% for T2, 53.6% for T3, and 33.3% for T4) and 67.7%, respectively. HDR-ISBT achieved good local control (80%) comparable with or superior to that of LDR-ISBT (65%) or mold therapy (85.7%, $P = 0.13$). Local control rates were higher in patients with early-stage lesions (T1/2 and/or localized). Severe late complications of Grade 3 or higher developed in 2 patients treated with LDR-ISBT.

HDR brachytherapy using molds

Nishimura *et al.* initiated a Phase I/II protocol to assess the toxicity and efficacy of HDR intracavitary brachytherapy [36] using molds in the treatment of squamous cell carcinoma of the oral cavity. A total of 8 patients with squamous cell carcinoma of the oral cavity were treated using this technique. The primary sites of the tumors included the buccal mucosa, oral floor, and gingiva. Two of the buccal mucosal cancers were located in the retromolar trigone. For each patient, a customized mold was fabricated, in which 2–4 after-loading catheters were placed for the Ir-192 HDR source, and 4–7 fractions of 3–4 Gy were administered 5 mm below the mold surface following EBRT of 40–60 Gy/2 Gy. The total dose of HDR brachytherapy ranged from 16–28 Gy. Although a good initial complete response rate of 7/8 (88%) was achieved, local recurrence was seen in 4 of these 7 patients. Marginal recurrence occurred in both of the retromolar trigone tumors. No serious late radiation damage (e.g. ulcer or bone exposure) has been observed thus far in the follow-up period of 15–57 months. The authors concluded that HDR brachytherapy using the mold technique is a safe and useful treatment method for early and superficial oral cavity cancer in selected patients. However, this treatment is not indicated for thick tumors and/or tumors located in the retromolar trigone.

Ariji *et al.* reported the usefulness of intraarterial chemotherapy in 4 patients with oral squamous cell carcinoma [37]. The molds were made from transparent acrylic resin, borrowing from a dental technique. The combined approach was applied as a boost therapy after EBRT. No tumor recurrence or radiation injury was observed in these 4 patients by the end of the follow-up period.

Obinata *et al.* presented a report of their clinical experience with HDR brachytherapy for head and neck cancer using a customized intraoral mold technique [38]. Two patients were treated with dental prostheses as the radiation carriers for HDR brachytherapy of head and neck cancer. HDR brachytherapy using a customized intraoral technique can be a viable treatment option for patients who are not candidates for surgery or EBRT. It was strongly suggested that specialized dentists are needed who are familiar with not only the anatomy and function of the head and neck region but also radiotherapy.

Kudor *et al.* introduced a novel customized intraoral mold treatment for maxillary gingival carcinoma [39]. Two patients with maxillary gingival carcinoma were treated using this technique as salvage therapy. The mold was designed using lead to shield normal soft tissues adjacent to the tumor from the radioactive source as much as possible. The radiation dose to the buccal mucosa and tongue was measured on the inner and outer surfaces of the intraoral mold before initiation of HDR brachytherapy by the remote after-loading system. The dose was reduced close to 10% of that applied to the tumor. No recurrence and no severe adverse effects to the normal soft tissue adjacent to the tumor were observed until the end of the follow-up period (2–8 months). HDR brachytherapy using the novel customized intraoral mold designed by Kudor *et al.* [39] might be a treatment option, not only in salvage therapy, but also in definitive therapy for maxillary gingival carcinoma.

Based on their experiences with 9 controlled cases, Chatani *et al.* [40] reported that mold therapy after chemoradiotherapy is a non-invasive procedure yielding a reproducible distribution of the radiation dose that closely fits the tumor volume. This technique seems to be a safe and effective treatment method for selected early and superficial squamous cell carcinomas of the oral cavity, although the indications for this treatment method are limited. Mold therapy after chemoradiotherapy may be indicated in

previously untreated superficial squamous cell carcinomas of the oral floor, soft palate, or gingiva, T1/2 tumors, and tumors showing complete response at the end of chemoradiotherapy.

Matsuzaki *et al.* showed that HDR brachytherapy using a customized mold is a minimally invasive treatment for oral cancer [41]; however, use of this technique for buccal mucosa and lip cancers involving the commissura labiorum is difficult for anatomical reasons. These authors introduced an improved customized mold with two added pieces to allow use of the mold at these sites. Five patients with buccal mucosa carcinoma and 1 patient with lip carcinoma were treated using this technique after EBRT. One patient with neck metastasis underwent both neck dissection and partial tumor resection before HDR brachytherapy. At the end of the follow-up period (2–40 months), no tumor recurrence had occurred in 5 patients, but 1 patient had suffered local recurrence. Thus, the study concluded that HDR brachytherapy using a customized mold is a viable therapeutic option for patients with buccal and lip carcinomas in whom the use of other therapeutic modalities is limited by age, performance status, and other factors.

HDR brachytherapy for postoperative, reirradiation, and palliative purposes

Postoperative brachytherapy is an elegant way to deliver adjuvant irradiation in cases with narrow or positive margins, including those with T4 tumors not involving the bone (Table 4) [1, 3]. The recommended postoperative dose in HDR brachytherapy is currently under investigation.

Glatzel *et al.* reported the results of a study using ISBT and endocavitary brachytherapy in recurrent head and neck cancer [42]. Between 1991 and 2000, 90 consecutive patients (68 men, 22 women) were treated with interstitial ($n=68$) or intracavitary ($n=22$) HDR brachytherapy in the head and neck area. Primary tumor locations were as follows: oropharynx ($n=26$), tongue/floor of mouth ($n=22$), nasopharynx ($n=10$), nose/paranasal sinuses ($n=9$), salivary glands ($n=5$), hypopharynx ($n=5$), and others ($n=8$). Carcinoma with unknown primary tumor location was also treated ($n=5$). HDR brachytherapy was administered to 51 patients with recurrent disease and 32 patients with residual tumor after primary chemoradiotherapy. HDR brachytherapy was also administered to 7 patients in primary palliative care. Each single dose per fraction ranged from 1.5–7.5 Gy (median, 5 Gy), and the total HDR brachytherapy dose ranged from 4–42 Gy (median, 17.5 Gy). The overall remission rate was 81%; complete remission was achieved in 46% of patients. No tumor change or progression was observed in 17 cases (19%).

Complete remission rates and median overall survival time differed in the three therapy groups. In cases of recurrent disease, complete remission was achieved in 28% of patients and the median overall survival time was 6 months. In cases of residual tumor, complete remission was achieved in 84% of patients and the median overall survival time was 25 months. For patients in primary palliative care, no complete remission was achieved, and the median overall survival time was 1 month. Late toxicity Grade 3 and 4 (RTOG score) occurred in 6 of the 90 (6.7%) patients. Glatzel *et al.* [42] concluded that HDR brachytherapy was an effective treatment modality in locoregional recurrent head and neck cancer. In cases with persistent or residual tumor after primary chemoradiotherapy, a local boost with brachytherapy improved the chance of complete remission from tumor disease.

Martínez-Monge *et al.* examined the feasibility of combined perioperative HDR brachytherapy and intermediate-dose EBRT as an alternative to full-dose adjuvant EBRT in patients with unirradiated squamous cell cancer of the oral cavity and oropharynx [43]. A total of 40 patients were treated with surgical resection and perioperative HDR brachytherapy at a dose of 4 Gy twice daily ×4 (16 Gy total) for R0 resections, and 4 Gy twice daily ×6 (24 Gy total) for R1 resections. EBRT (45 Gy/25 fractions) was performed postoperatively. Patients with Stage III and IVa tumors and some recurrent cases received concomitant cisplatin-paclitaxel chemotherapy during EBRT. The rate of protocol compliance was 97.5%; 11 patients (27.5%) developed toxicity of RTOG Grade 3 or higher; 4patients (10%) presented complications requiring a major surgical procedure (RTOG 4); 1 patient died due to excessive blood loss (RTOG 5). Three complications (7.5%) occurred in the perioperative period, and 8 (20.0%) occurred more than 3 months after completion of the treatment program. Severe complications were more frequent in posteriorly located implants than in anterior implants ($P=0.035$). After a median follow-up time of 50 months for living patients (range, 2.5–86.1 +), the 7-year actuarial rates of local and locoregional control were 86% and 82%, respectively, and the 7-year disease-free survival and overall survival rates were 50.4% and 52.3%, respectively.

The study of Martínez-Monge *et al.* [43] demonstrated that perioperative HDR brachytherapy can be integrated into the management of patients with resected cancer of the oral cavity who are candidates to receive postoperative radiation or chemoradiation. Local control and toxicity rates were similar to those expected after standard chemoradiation. Perioperative HDR brachytherapy was associated with high toxicity in posterior locations; thus, the scheduled perioperative HDR brachytherapy dose was adjusted to the closest lower level.

Do *et al.* reviewed their experience with patients with T4N0–3M0 locally advanced oral cavity and oropharyngeal squamous cell carcinoma who underwent definitive chemoradiotherapy or radiotherapy followed by HDR brachytherapy [44]. Radiotherapy doses ranged from 45–50.4 Gy. Patients were reassessed after receiving the first dose, and if

Table 4. Results of HDR brachytherapy for boost, recurrence or reirradiation

Author (year), Institute	¶PTNO	Group	Treatment	§Schedule	†Local control	Toxicity
Post operative Bx						
Glatzel (2002) [42], Sulh, Germany	90 22 Oral	51 Recurrence	11END[1]* + 40 ISBT[2]*	EBRT 37 Gy (30–60) + Bx 19.7 Gy (5–42 Gy)	CR 28% (MST6mo)	6.7% RTOG G3-
		32 Boost/residual	10 END + 21 ISBT	EBRT 59.3 Gy (42–70 Gy) + Bx 12.9 Gy (4–37.5 Gy)	84% (25m)	
		7 Palliation	7 ISBT	Bx 23.9 Gy (4–37.5 Gy)	0% (1m)	
Martinez-Monge (2008) [43], Navarre, Spain	40 28 Oral	Primary 34		Surgery + EBRT 45 Gy + Bx 16–24 Gy	82% LRC (7y)	15% RTOG G3, 10% G4, 2.5% G5
		Recurrence 6				
Do (2009) [44], Long beach, USA	20 T4N0–3 10 Oral	Boost for T4 tumor	14CRT⇒BT	45–50.4 Gy EBRT + platinum + Bx 3–4 Gy × 8–10	61%	30% S, 5% B, other**
			6RT⇒BT			
Reirradiation			**Previous treatment**			
Donath (1995) [31], McGill Univ., Canada	16 6 Oral	Postop adjuvant	EBRT 50 Gy –	3 Gy × 8	4 local rec	1 fistula, 8 surgery
		12 positive margin			3 NED (5–16 mo)	
Krüll (1999) [45], Hamburg, Germany	19 (11 rec 8 PD) 13 Oral, 6 OPC	2T1, 5T2, 6T3, 6T4	EBRT 50–76.5 Gy	10 Gy once a week	5 CR	1S
		13N +		2 10 Gy, 12 20 Gy, 5 30 Gy	34% (2 y)	
Hepel (2005) [46], Long Beach, USA	30 (36 sites) 7 Oral		EBRT 59 Gy (23–75 Gy)	Bx 3–4 Gy × 3–12 (18–48 Gy)	69%	G 3/4 late 16%
				Mucosal site 3 Gy/fr and non-mucosal site 4 Gy/fr	57% (tongue)	
Narayana (2007) [47], MSK, USA	30	18 OP + Bx	23 EBRT 20–40 Gy	3.4 Gy × 10	71% (2 y)	6G2 4G3 in OP + BT
	6 Oral	3 EBRT + Bx 9 sole Bx		EBRT 39.6 Gy + Bx 4 Gy × 5 Bx 4 Gy × 10	88% OP + Bx > 40% EBRT ± Bx, $P = 0.05$	
Schiefke (2008) [48], Leipzig, Germany	13 rec Oral 9	2 Sole BT 2	11 PT EBRT 60–69.9 Gy	EBRT 60–69.9 Gy + Bx 3 Gy × 10 (21–36 Gy)	80% (2y)	Early 61% S 1, B 2, other***
Bartochowska (2011) [49], Poznań, Poland	106 PDR + 50 HDR	8 CRT, 16 HT	142 PT (91%) EBRT	HDR 3–6 Gy × 3–10 (12–30 Gy)	37.7% CR + PR (MFT 6 Mo)	35%
	Oral (23 PDR + 17 HDR)	142 reirradiation		PDR 20 Gy (20–40 Gy)	17% OS (2 y)	

PTNO = number of patients, EBRT = external body irradiation, Bx = brachytherapy, OPC = oropharyngeal cancer, CR = complete response, PR = partial response, S = ulcer soft tissue (including early complication), B = bone exposure and/or necrosis, MST = median survival time, MFT = median follow-up period, END = endocavitary brachytherapy (nasopharyngeal and nasal carcinoma), ISBT = interstitial brachytherapy, MSK = Memorial Sloan-Kettering Cancer Center, HT = interstitial hyperthermia, G = grade, LRC = locoregional control, OP = surgery, CRT = chemoradiotherapy, 1*5.0 Gy (range, 3.0–7.5 Gy) twice a week, (3.0 Gy) or weekly (5.0–7.5 Gy, 19 patients)

*Metal needles 11PT single dose 5.0–Gy (1 PT 7 Gy, 1 Pt 7.5 Gy) once a week. Plastic tubes single dose 3.0 Gy (1.5–7.5 Gy) daily or twice a day

4 dysphasia, 2 xerostomia, 1 tube feeding, 2 hoarseness, * 2 nerve palsy, 4 wound healing disorder, ¶HDR unless otherwise stated, §twice a day treatment unless otherwise stated, †5 y unless otherwise stated

the response was inadequate, brachytherapy was performed at doses ranging from 24–30 Gy at 3–4 Gy/fraction twice daily with 6 h between fractions. Concurrent chemotherapy was platinum-based. In their study, 20 patients were treated with chemoradiotherapy or radiotherapy alone followed by brachytherapy. Soft tissue invasion was observed in 13 patients, bone and cartilage invasion was observed in 7, 14 patients were treated with chemoradiotherapy followed by brachytherapy, and 6 patients were treated with radiotherapy alone followed by brachytherapy. The 5-year locoregional control was 61%. The 5-year overall survival was 29%. When patients treated with EBRT alone were excluded, the 5-year overall survival was 36%. Nodal status was the only prognostic factor. The study of Do *et al.* [44] suggests that chemoradiotherapy followed by HDR brachytherapy is a feasible treatment option for patients with T4 locally advanced cancer of the oral cavity and oropharynx. In patients with poor response to chemoradiotherapy, HDR brachytherapy may be used for dose escalation to increase locoregional control.

Donath *et al.* utilized HDR in a postoperative adjuvant setting following wide local excision of tumors in patients who presented with recurrent disease ($n = 12$) or a second primary tumor site in the head and neck ($n = 4$) [31]. All patients had previously received EBRT to the head and neck. Due to this previous course of irradiation, only 8 treatments of 3 Gy each were delivered, for a total of 24 Gy over a period of 4 days. However, during the follow-up period of 2–16 months, only 3 patients remain disease-free.

Krüll *et al.* reported on 19 patients with progressive or recurrent head and neck cancer, who had been treated with HDR-ISBT [45]. All patients had previously undergone EBRT. Initial therapy also included surgery in 9 cases and chemotherapy in 3 patients. Staging according to the TNM system revealed advanced stage tumors in the majority of patients. Interstitial brachytherapy was carried out with the isotope Ir-192. The applied total dose at the reference isodose varied from 10–30 Gy. Application was fractionated once a week. Complete remission was achieved in 5 patients and partial remission was achieved in 10 patients. In 4 patients, the tumor continued to grow despite administration of HDR brachytherapy. The mean follow-up time in this study was 21 months. The local control rate was 34% at 24 months. The survival rate was 49% at 12 months and 35% at 24 months. Krüll *et al.* [45] recommended HDR-ISBT as a palliative treatment in preirradiated squamous cell carcinoma with local recurrence or progression.

Hepel *et al.* reported their experiences with reirradiation using HDR brachytherapy in 30 patients [46]. All patients had inoperable cancer, refused surgery, or had gross residual disease after salvage surgery for recurrent disease. In the 30 patients, 36 sites were implanted by application of HDR-ISBT at a mean tumor dose of 34 Gy (18–48 Gy) in twice daily fractions of 3–4 Gy/fraction. Local tumor control was achieved in 69% of implanted sites. Overall survival at 1 and 2 years was 56% and 37%, respectively. Grade 3/4 late complications occurred in 16% of the patients. No fatal complications were observed. Hepel *et al.* [46] concluded that although HDR-ISBT has a potential to cure a part of oral cancer recurrences, only superficial small tumors can be treated at this time, partly because of the inexperience of health care providers.

Narayana *et al.* reported the preliminary results of a study including 30 patients with recurrent head and neck cancer treated with HDR-ISBT [47] between September 2003 and October 2005. Local or regional recurrence in the area of previous EBRT was evident in 77% (23/30) of patients. Treatment sites included the oral cavity/oropharynx (11/30), neck (10/30), face/nasal cavity (6/30), and parotid bed (3/30). Whereas 18 patients underwent surgical resection followed by HDR-ISBT, 3 patients were treated with combined EBRT and HDR-ISBT, and the remaining 9 were treated with HDR-ISBT alone. The dose and fractionation schedules were as follows: 3.4–34 Gy twice daily for postoperative cases, 4–20 Gy twice daily when combined with 40–50 Gy EBRT, and 4–40 Gy twice daily for definitive treatment. HDR-ISBT was initiated 5 days after catheter placement to allow for tissue healing.

During the median follow-up period of 12 months, 6 local recurrences were observed 1–10 months after completion of the procedure. The 2-year local control and overall survival rates for the entire group were 71% and 63%, respectively. Patients treated with surgical resection and HDR-ISBT had better 2-year local control rates compared with the patients treated with HDR-ISBT ± EBRT alone (88% vs 40%, $P = 0.05$). Six Grade 2 and four Grade 3 complications were noted in 5 patients, all in the postoperative HDR-ISBT group. The preliminary results of the study of Narayana *et al.* [47] on HDR brachytherapy indicated acceptable local control and morbidity in recurrent head and neck cancers using this treatment method. Planned surgical resection followed by HDR brachytherapy was associated with improved tumor control in the high-risk patients in this study.

Schiefke *et al.* examined the potential of HDR-ISBT to improve safety and survival after surgical resection [48]. From 2000–2006, 13 patients with pretreated, recurrent head and neck cancer (oral, maxillary sinus, lips) were treated with a curative approach by resection of the recurrent tumor and subsequent HDR-ISBT. Treatment included coverage of the surgical defect and sealing of the brachytherapy applicators with free microvascular or myocutaneous flaps. Conventional radiotherapy and chemotherapy were added as required. The patient group was evaluated with respect to survival and outcome. Additionally 5 patients who received combination therapy for primary carcinomas were included in this report in order to evaluate the rate of complications and adverse effects. Kaplan–Meier

curves revealed a 2-year overall survival rate of 65.3%. The mean survival time for recurrent carcinomas was 22.8 months. Patients treated for primary carcinoma had a mean survival time of 34.5 months. Of the 5 patients with primary head and neck cancer, 4 (80%) were alive and without evidence of disease 2 years after treatment. The acute and chronic adverse side effects were manageable. No relevant complications concerning tissue transfer were observed. Schiefke *et al.* [48] concluded that surgical resection combined with HDR-ISBT can lead to long-term remission, and that simultaneous microvascular defect reconstruction provides tissue cover for brachytherapy.

Bartochowska *et al.* reported the results of HDR- and PDR-ISBT in the palliative treatment of patients with locally or regionally recurrent head and neck cancers [49]. PDR- and HDR-ISBT were used in 106 and 50 patients, respectively, from January 2002 to November 2008. In 8 patients, brachytherapy procedures were performed in combination with simultaneous chemotherapy (details were not shown). Sixteen patients were additionally treated with interstitial hyperthermia. All patients were regularly followed up within 6 months of final treatment. Local control, complication, and survival rates were assessed. Complete remission and partial remission 6 months after final treatment were achieved in 37.7% of patients, whereas survival rates 12 and 24 months after brachytherapy were 40% and 17%, respectively. The overall complication rate was 35%. The results of the study by Bartochowska *et al.* [49] suggest that HDR- and PDR-ISBT are safe alternatives in the palliative treatment of patients with locally or regionally recurrent head and neck cancers with relapse in a previously irradiated area who were not qualified for, or rejected surgery. These treatments offer a good palliative effect with acceptable complication rates.

DISCUSSION

The oral cavity is essential in coordinating the complex functions of deglutition, phonation and airway protection. Preserving its function is a difficult challenge when treating carcinoma in this anatomical region. The treatment modalities available include surgery, EBRT, brachytherapy and various combinations of the three. The wide range of results in the literature leaves considerable uncertainty as to the treatment of choice, but years of experience in the treatment of head and neck tumors with radiotherapy has demonstrated that a high tumor dose is required to achieve local control.

Sresty *et al.* reported that the ISBT treatment modality produces equal or superior planning results when compared with intensity-modulated radiation therapy (IMRT) [50]. Fifteen patients with tongue cancer treated with HDR-ISBT were replanned. Tongue cancer was evaluated using the IMRT planning system. Contouring of target volume, including all critical structures, was done using the IMRT treatment planning system to closely match the implant brachytherapy planning system. Prescription goals were specified and treatment plans generated. The conformity index and doses to critical organs were then calculated and compared between IMRT and ISBT. Planning time was also recorded for both the techniques in all the cases. Very good dose conformity was observed in ISBT, similar to that observed in IMRT. Dose to critical structures was lower in ISBT in all cases. Planning time was also less in ISBT for many cases. These results encouraged the authors to continue ISBT [50]. They concluded that ISBT is an ideal solution for high-dose delivery exclusively to the primary tumor volume, while limiting the risks of severe xerostomia or trismus [1, 3, 6].

HDR hyperfractionated ISBT has the following advantages: (i) accurate calculations made possible by complete fixation of the guide tubes, (ii) parallel source arrangement with the sophisticated technique, (iii) homogeneous dose distribution due to stepping source optimization, (iv) better patient care in normal wards with elimination of radiation exposure to medical staff, administration on an outpatient basis in several cases, and (v) shorter treatment times than with EBRT. Future uses of HDR-ISBT include the introduction of a 3D image-based approach for GTV and CTV assessment. Development is in progress of a common language to describe the concepts and define the terms to be used in this promising field [1].

HDR-ISBT treatment should be executed carefully, because the short treatment times allow no time for correction of errors that could result in harm to patients. Hence all personnel involved in HDR brachytherapy must be well trained and constantly alert during treatment delivery [28]. The development of well-controlled randomized trials addressing issues of efficacy, toxicity, quality of life, and costs-versus-benefits will ultimately define the role of HDR brachytherapy [28].

One of the limitations of HDR-ISBT is a lack of experience. For example, studies examining prognostic factors in LDR-ISBT allowed improvement of the technique. Treatment now involves leaded protection of the mandible, optimal intersource spacing (1.2–1.4 cm), calculations of volume treated (30 cm^3, i.e. three loops), accurate safety margins (5 mm), and effective dose rates (0.5 Gy/h). The total dose [65 Gy in brachytherapy alone, 25 Gy in combination with EBRT (50 Gy) in primary carcinomas of the oral cavity, 60 Gy in recurrent cancer in previously irradiated tissues] and an optimal interval between EBRT and brachytherapy (<20 days) have also been determined for LDR-ISBT [1, 3, 6]. Those factors remain to be established for HDR-ISBT.

PDR-ISBT appeared to be functionally equivalent to continuous ISBT. The results of PDR-ISBT should improve with better dose rate control and optimization of the dose

distribution [51, 52]. Brenner *et al.* reported the superiority of daytime PDR-ISBT over continuous LDR-ISBT [51]. However, if PDR-ISBT is applied with curative intent, the treatment unit is unavailable for treatment of other patients. As HDR-ISBT remote-controlled after-loading units are not available at all institutions, and many patients require treatment with the units that are available, continuous LDR-ISBT and daytime PDR-ISBT are difficult to perform for patients with head and neck cancer.

Due to the paucity of evidence in the literature, and the fact that few institutions are equipped to test the potential of HDR-ISBT for the convenience of patients and medical staff, the future of HDR-ISBT is uncertain. However, many studies conclude that this therapeutic mode should be explored further. In summary, although more concrete evidence is warranted, HDR-ISBT may be an important option for treatment of oral cancer.

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Dose-Volume Histogram Predictors of Chronic Gastrointestinal Complications After Radical Hysterectomy and Postoperative Concurrent Nedaplatin-Based Chemoradiation Therapy for Early-Stage Cervical Cancer

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Summary

In this study, dose-volume histogram parameters of the small bowel loops were predictive for the development of chronic gastrointestinal (GI) complications after postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer. Multivariate analysis indicated that V40 (volume receiving more than 40 Gy) of the small bowel loops and smoking were independent predictors of GI complications.

Purpose: The purpose of this study was to evaluate dose-volume histogram (DVH) predictors for the development of chronic gastrointestinal (GI) complications in cervical cancer patients who underwent radical hysterectomy and postoperative concurrent nedaplatin-based chemoradiation therapy.

Methods and Materials: This study analyzed 97 patients who underwent postoperative concurrent chemoradiation therapy. The organs at risk that were contoured were the small bowel loops, large bowel loop, and peritoneal cavity. DVH parameters subjected to analysis included the volumes of these organs receiving more than 15, 30, 40, and 45 Gy (V15-V45) and their mean dose. Associations between DVH parameters or clinical factors and the incidence of grade 2 or higher chronic GI complications were evaluated.

Results: Of the clinical factors, smoking and low body mass index (BMI) (<22) were significantly associated with grade 2 or higher chronic GI complications. Also, patients with chronic GI complications had significantly greater V15-V45 volumes and higher mean dose of the small bowel loops compared with those without GI complications. In contrast, no parameters for the large bowel loop or peritoneal cavity were significantly associated with GI complications. Results of the receiver operating characteristics (ROC) curve analysis led to the conclusion that V15-V45 of the small bowel loops has high accuracy for prediction of GI complications. Among these parameters, V40 gave the highest area under the ROC curve. Finally, multivariate analysis was performed with V40 of the small bowel loops and 2 other clinical parameters that were judged to be potential risk factors for chronic GI complications: BMI and smoking. Of these 3 parameters, V40 of the small bowel loops and smoking emerged as independent predictors of chronic GI complications.

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Conclusions: DVH parameters of the small bowel loops may serve as predictors of grade 2 or higher chronic GI complications after postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer. © 2013 Elsevier Inc.

Introduction

Adjuvant whole-pelvic radiation therapy (RT) after radical hysterectomy reduces locoregional recurrence in cervical cancer patients after surgery with adverse risk factors (1, 2). However, patients undergoing whole-pelvic RT after radical hysterectomy may suffer severe gastrointestinal (GI) complications with an incidence varying from 3%-13% for patients treated with pelvic RT alone (1-3). Moreover, while adjuvant concurrent chemoradiation therapy has been shown in several studies to improve survival rates for high-risk cervical cancer patients compared with adjuvant RT alone, GI complications were observed more frequently in conjunction with concurrent chemoradiation therapy than with RT alone (4). Therefore it is important to improve the feasibility of adjuvant concurrent chemoradiation therapy by reducing GI complications.

Because the small bowel is one of the critical organs involved in GI complications, a predictive model of acute GI complications of the small bowel has been established with the aid of Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) (5). However, the correlation between dose-volume effect and chronic GI complications of the small bowel has not been extensively investigated.

Since 2000, we have been using postoperative concurrent nedaplatin-based chemoradiation therapy for early-stage cervical cancer patients with adverse risk factors (6). The purpose of the study reported here was to evaluate dose-volume histogram (DVH) predictors for the development of chronic GI complications in cervical cancer patients who underwent radical hysterectomy and postoperative concurrent nedaplatin-based chemoradiation therapy.

Methods and Materials

Patients

A total of 131 patients with cervical cancer received radical hysterectomy and postoperative RT at our institute between April 2000, when we started to use postoperative concurrent nedaplatin-based chemoradiation therapy, and September 2010. Treatment criteria for postoperative RT were previously described (6, 7). Thirty-four of these patients were excluded from the study: 18 who received extended-field radiation therapy alone because of multiple lymph node metastases (7), 9 who refused concurrent chemotherapy, 3 who received intracavitary brachytherapy with whole-pelvic RT because of a close surgical margin, and 4 early patients who did not undergo radiation treatment planning computed tomography (CT) with a 2-dimensional (2D) era. The remaining 97 patients treated with concurrent chemoradiation therapy were analyzed for this study with a minimum follow-up period of 3 months. This study was approved by our institutional review board.

Radiation therapy and chemotherapy

Whole-pelvic RT was delivered with 2D planning in 65 patients between April 2000 and March 2008 and with 3-dimensional (3D) conformal treatment planning in 32 patients starting April 2008. During the 2D era, RT was delivered using 10-megavolt X rays from a linear accelerator with the anteroposterior parallel opposing technique. The superior margin of the whole-pelvic RT was at the upper edge of the fifth lumbar vertebra and the inferior margin was the inferior edge of the obturator foramen. Laterally, the field extended 2 cm beyond the lateral margins of the bony pelvic wall. After we defined an isocenter or field-shape in the X-ray simulator, CT with the isocenter position marked was performed with 5.0-mm slices without filling the bladder to calculate the monitor unit and check the dose distribution. The CT scan range was from the upper edge of L3 to at least 7 cm below the bottom of the obturator foramen. The dose distribution was calculated using a commercial treatment planning system (FOCUS; Elekta, Stockholm Sweden). The prescribed RT doses were 50 Gy administered in 25 fractions over 5 weeks at the center of the body. Multileaf collimators were used to block the upper and lower corners of the radiation field. No target volume or organ at risk was delineated before treatment. Since April 2008, all patients have been treated with 3D conformal treatment planning. RT planning CT was performed with 2.5-mm slices with normal quiet breathing and a full-bladder scan. The CT scan range was the same as that used in 2D planning. A commercial treatment planning system (XiO TPS; Elekta) was used to design the radiation fields. The clinical target volume (CTV) comprised a central vaginal CTV and a regional nodal CTV. The former included the proximal vagina and paravaginal tissues and the latter consisted of the common iliac, external and internal iliac, and presacral lymph nodes. CTVs were contoured according to the consensus guidelines of the Radiation Therapy Oncology Group (RTOG) 0418 (8) and its atlas on the RTOG website. The planning target volume (PTV) was generated by using 1.0-cm uniform expansion of the CTV. The prescribed RT doses were 50 Gy at the center of the PTV, administered in 25 fractions over 5 weeks by means of the 3D 4-field box technique. Multileaf collimators were used to cover the PTV with a margin of approximately 5 mm. No organ at risk was delineated before treatment. Nedaplatin (40 mg/m^2) was given intravenously on a weekly basis during the course of whole-pelvic RT for 5 weeks as previously described (6).

Contouring and evaluation of normal structures

The organs at risk that were contoured comprised the small bowel loops, large bowel loop, and peritoneal cavity. All contouring was done retrospectively. The superior and inferior extents of critical organs were outlined on all CT slices containing portions of the PTV (3D) or field margins (2D), including an additional area 2-cm superior and inferior to the limit of the PTV or field margins. Therefore, the organs at risk, including the large bowel loop, small bowel loops, and peritoneal cavity, could not be contoured in full volume. The large bowel loop was contoured first as a single loop continuing from the end of the sigmoid colon to the ascending colon, and the remaining bowel loops were classified as the small bowel loops. A preoperative diagnostic CT scan using oral and intravenous contrast media was performed in 92/97 patients (95%). This preoperative CT scan

was displayed when the organs at risk were contoured using postoperative radiation treatment planning CT. Diagnostic CT images were not fused to the planning scans. In the remaining 5 patients, postoperative radiation treatment planning CT only was used for contouring of the organs at risk. The peritoneal cavity was defined as including the volume surrounding the small bowel loops out to the edge of the peritoneum. The boundaries included the abdominal wall anteriorly and anterolaterally, the retroperitoneal and deep pelvic muscles posterolaterally, and the great vessels, vertebral bodies, and sacrum posteriorly. The rectum and bladder were excluded from the peritoneal cavity volume. DVH parameters subjected to analysis included the mean doses to the small bowel loops, large bowel loop, and peritoneal cavity, and the volumes of these organs receiving more than 15, 30, 40, and 45 Gy (V15-V45).

Follow-up and evaluation of chronic GI complications

The patients were followed up by gynecologic and radiation oncologists on an outpatient basis every month in the first year, every 2 months in the second year, every 3 months in the third year, every 4 months in the fourth year, every 6 months in the fifth year, and annually thereafter until 10 years after treatment. We defined a chronic complication as a GI event that occurred more than 3 months after radiation therapy was started. The severity of the GI complication was classified according to the RTOG/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Score. Toxicity data including the grade of GI complications were collected retrospectively through hospitalization and follow-up records.

Statistical analysis

Associations between selected DVH parameters (V15, V30, V40, V45, and mean dose) and the incidence of grade 2 or higher chronic GI complications were evaluated. The relationships between clinical or DVH parameters and the incidence of chronic GI complications were analyzed with the Mann-Whitney *U* test for quantitative variables and the Fisher exact test for categorical variables. The mean DVH parameters for the small bowel loops, large bowel loop, and peritoneal cavity of patients with and without GI complications were compared by Mann-Whitney *U* test. Receiver operating characteristics (ROC) curve analysis of each of the DVH parameters was performed to select the most relevant threshold for prediction of a grade 2 or higher chronic GI complication. The predictive value of a parameter was evaluated based on the area under the ROC curve (AUC). The AUC reflects the ability of the test to distinguish between patients with and without disease. The optimal threshold for each DVH parameter was defined as the point yielding the minimal value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$, which is the point on the ROC curve closest to the upper left-hand corner (9). Multivariate analysis using Cox regression models was performed to identify risk factors associated with grade 2 or higher chronic GI complications. The actuarial incidence of GI complications was calculated with the Kaplan-Meier method and differences between groups were compared by log-rank test. A P value of $<.05$ or a 95% confidence interval not encompassing 1 was considered to be statistically significant. All statistical tests were 2-sided.

Results

The characteristics of the 97 patients are shown in Table 1. The median follow-up period from the start of radiation therapy was 43 months (range 4-111 months). None of the patients experienced a local or distant recurrence within 3 months. The Eastern Cooperative Oncology Group performance status was 0-1 for all patients. The median age of the patients was 51 years old (range 28-70 years old). Twenty-three patients (24%) had a history of smoking, with a median Brinkman index (number of cigarettes per day × smoking years) of 400 (range 100-1200). The median total dose of nedaplatin was 285 mg (range 30-375 mg). Ninety-two patients (95%) received the whole RT dose as planned (50 Gy), but 3 patients (3%) received only 46 Gy and 2 (2%) received 44 Gy because of neutropenia (4 patients) or patient refusal (1 patient). Eighty-one patients (84%) had grade 0-1, 6 (6%) had grade 2, and 10 (10%) had grade 3 chronic GI

Table 1 Patient and treatment characteristics

	No. (%)
Age (y)	
Mean	51
SD	±10
T-stage	
T1	53 (55)
T2	44 (45)
N-stage	
N0	64 (66)
N1	33 (34)
Histology	
SCC	71 (73)
Ad	24 (25)
Others	2 (2)
Smoking	
None	74 (76)
Yes	23 (24)
Diabetes	
None	94 (97)
Yes	3 (3)
Abdominopelvic surgery	
None	94 (97)
Yes	3 (3)
BMI (kg/m^2)	
Mean	21.6
SD	±3.8
RT total dose (Gy)	
50	92 (95)
46	3 (3)
44	2 (2)
RT technique	
2D	65 (67)
3D	32 (33)
Total nedaplatin (mg)	
Mean	274
SD	±52

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; Ad = adenocarcinoma; BMI = body mass index; RT = radiation therapy; SCC = squamous cell carcinoma; SD = standard deviation.

Table 2 Univariate analysis (Mann-Whitney *U* test and Fisher exact test) for the development of grade 2 or higher chronic GI complications

Variable	Grade 0-1 No.	Grade 2-3 No.	*P* value
Age (y)			
<52	39	10	.294
≥52	42	6	
Total nedaplatin (mg)			
<285	39	8	.892
≥285	42	8	
T-stage			
T1	46	7	.338
T2	35	9	
N-stage			
N0	53	11	.798
N1	28	5	
Histology			
SCC	60	11	.660
Non-SCC	21	5	
RT total dose			
50 Gy	76	16	.308
<50 Gy	5	0	
RT technique			
2D	57	8	.133
3D	24	8	
Smoking			
None	66	8	.005
Yes	15	8	
BMI (kg/m^2)			
<22	43	14	.011
≥22	38	2	

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; BMI = body mass index; GI = gastrointestinal; RT = radiation therapy; SCC = squamous cell carcinoma.

Table 3 Comparison of mean DVH parameters of the small bowel loops, large bowel loop, and peritoneal cavity in patients with and without chronic GI complications (Mann-Whitney *U* test)

	Overall	Grade 0-1	Grade 2-3	*P* value
		Small bowel loops		
		Mean volume ± SE (mL)		
V15	337 ± 15	299 ± 13	527 ± 37	<.001
V30	308 ± 13	273 ± 11	485 ± 29	<.001
V40	289 ± 13	255 ± 11	458 ± 27	<.001
V45	280 ± 12	247 ± 11	444 ± 26	<.001
		Mean dose (cGy ± SE)		
	3,523 ± 80	3,429 ± 86	3,994 ± 160	<.001
		Large bowel loop		
		Mean volume ± SE (mL)		
V15	241 ± 12	241 ± 12	239 ± 34	.730
V30	207 ± 10	210 ± 11	192 ± 23	.550
V40	183 ± 10	189 ± 11	156 ± 17	.331
V45	176 ± 9	182 ± 10	149 ± 16	.321
		Mean dose (cGy ± SE)		
	2,747 ± 62	2,768 ± 66	2,639 ± 174	.487
		Peritoneal cavity		
		Mean volume ± SE (mL)		
V15	1,151 ± 29	1,129 ± 32	1,262 ± 70	.111
V30	1,045 ± 25	1,027 ± 27	1,138 ± 64	.174
V40	974 ± 25	960 ± 27	1,049 ± 65	.336
V45	941 ± 24	927 ± 26	1,013 ± 65	.343
		Mean dose (cGy ± SE)		
	3,421 ± 47	3,387 ± 50	3,596 ± 122	.169

Abbreviations: DVH = dose-volume histogram; GI = gastrointestinal; SE = standard error; V15-45 = volume receiving more than respective dose.

complications. Of the 10 patients with grade 3 GI complications, 5 (5% of all patients) had small bowel obstruction requiring surgery.

The incidence of chronic GI complications was analyzed as a function of clinical factors. Because there were few patients with diabetes or a history of abdominopelvic surgery among the study population, we did not analyze these factors. The results of univariate analyses are shown in Table 2. Smoking habit and low body mass index (BMI; <22) were significantly associated with grade 2 or higher GI complications. The mean DVH parameters of the small bowel loops, large bowel loop, and peritoneal cavity of patients with and without GI complications are shown in Table 3. Patients with grade 2 or higher GI complications had significantly greater V15-V45 volumes in the small bowel loops than did those without GI complications ($P<.001$). The mean dose to the small bowel loops differed significantly for patients with and without GI complications (39.94 vs 34.29 Gy, $P<.001$). In contrast, none of the parameters for the large bowel loop or peritoneal cavity were significantly associated with GI complications.

ROC curve analysis was performed to select the most relevant parameter to identify predictors of grade 2 or higher chronic GI complications among DVH parameters for the small bowel loops. The results are shown in Table 4. Because AUCs for mean dose, V15, V30, V40, and V45 were 0.693, 0.909, 0.912, 0.921, and 0.890, respectively, indicating that V15-V45 have good accuracy for prediction of GI complications. Strong collinearity among V15-V45 was expected in multivariate

Table 4 ROC curve analysis for DVH parameters of small bowel loops in relation to grade 2 or higher chronic GI complications

	AUC	95% CI	Optimal threshold: Value	Optimal threshold: Sensitivity/specificity (%)
Mean dose	0.693	0.580-0.806	3600 cGy	62.5/62.5
V15	0.909	0.855-0.963	380 mL	93.8/82.1
V30	0.912	0.857-0.967	360 mL	93.8/82.1
V40	0.921	0.869-0.972	340 mL	87.5/87.2
V45	0.890	0.819-0.962	340 mL	87.5/85.1

Abbreviations: AUC = area under the ROC curve; CI = confidence interval; DVH = dose-volume histogram; GI = gastrointestinal; ROC = receiver operating characteristics; V15-45 = volume receiving more than respective dose.

Table 5 Multivariate analysis for the development of grade 2 or higher chronic GI complications

Variable	HR (95% CI)	*P* value
V40 of small bowel loops (mL)	1.012 (1.007-1.018)	<.001
BMI (<22 vs ≥22)	3.024 (0.585-15.622)	.187
Smoking (yes vs no)	3.103 (1.023-9.415)	.046

Abbreviations: BMI = body mass index; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; V40 = volume receiving more than 40 Gy.

analysis. Therefore, we used V40 of the small bowel loops in multivariate analysis because this parameter had the highest AUC value. The optimal threshold for V40 was 340 mL. Thus, multivariate analysis was performed with V40 of the small bowel loops and 2 other clinical parameters that were judged to be potential risk factors for chronic GI complications: BMI and smoking habit. Of these 3 parameters, V40 of the small bowel loops and smoking emerged as independent predictors of GI complications (Table 5).

The overall incidences of grade 2 or higher GI complications were 0% (0/39), 7% (2/29), and 48% (14/29) for patients with V40 values of <250 mL, 250-340 mL, and >340 mL, respectively. Thus, the overall incidence of grade 2 or higher GI complications increased in a volume-dependent manner. Therefore, we performed Kaplan-Meier estimates of the cumulative incidence curves for grade 2 or higher chronic GI complications stratified by V40 of the small bowel loops using the above intervals. The cumulative incidence curves for grade 2 or higher chronic GI complications stratified by V40 of the small bowel loops are shown in Fig. The 3-year cumulative incidences of grade 2 or higher GI complications were 0%, 8.4%, and 46.2% for patients with V40 values of <250 mL, 250-340 mL, and >340 mL, respectively, with a significantly higher risk for patients with V40 > 340 mL than for the other groups ($P<.001$).

Discussion

Several previous studies have introduced predictive factors potentially associated with chronic GI complications after RT for gynecologic malignancies employing several types of therapy (3, 10-14). These factors include total RT dose, RT dose per fraction, history of diabetes, acute toxicity, BMI, age, previous abdominopelvic surgery, and smoking. In our study, smoking and low BMI were identified by univariate analysis as predictors of GI complications. Moreover, the V15-V45 volumes and the mean dose of the small bowel loops all showed a significant association with chronic GI complications. In addition, multivariate analysis identified V40 of the small bowel loops and smoking as independent predictors of GI complications. To the best of our knowledge, ours is the first study to show that DVH parameters of the small bowel loops derived with an up-to-date approach are associated with chronic GI complications after postoperative concurrent chemoradiation therapy for cervical cancer.

We believe that our findings are important for the practice of the radiation oncology, because adverse events caused by radiation exposure, such as GI complications, may be relieved by using an appropriate radiation technique or a mechanical device such as a belly-board. Recently, intensity modulated radiation therapy (IMRT) has emerged as a sophisticated technique for treatment of tumor regions or areas at risk of recurrence, while sparing adjacent normal tissue from high-dose irradiation, including in patients with gynecological cancer treated with IMRT after radical hysterectomy (15-18).

Two methods for contouring the small bowel volume have been reported: one uses direct delineation of the individual loops, whereas the other bases delineation on the peritoneal cavity because the bowel may lie within this space at any time throughout the course of treatment (5). Because these methods have not been compared to determine which leads to better predictions of chronic complications of the small bowel, we established separate parameters for the irradiated volume of the small bowel loops and the peritoneal cavity to examine which parameters correlated with

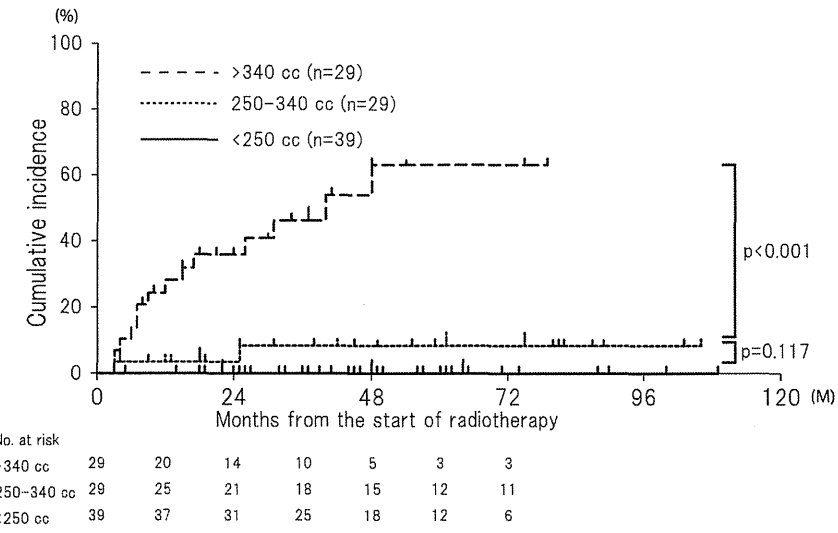

Fig. Kaplan-Meier estimates of cumulative incidence curves for grade 2 or higher chronic gastrointestinal (GI) complications stratified by V40 of the small bowel loops. The 3-year cumulative incidences of grade 2 or higher GI complications were 0%, 8.4%, and 46.2% for patients with V40 values of <250 mL, 250-340 mL, and >340 mL, respectively, with a significantly higher risk for patients with V40 > 340 mL than for the other groups (log-rank test; $P<.001$).