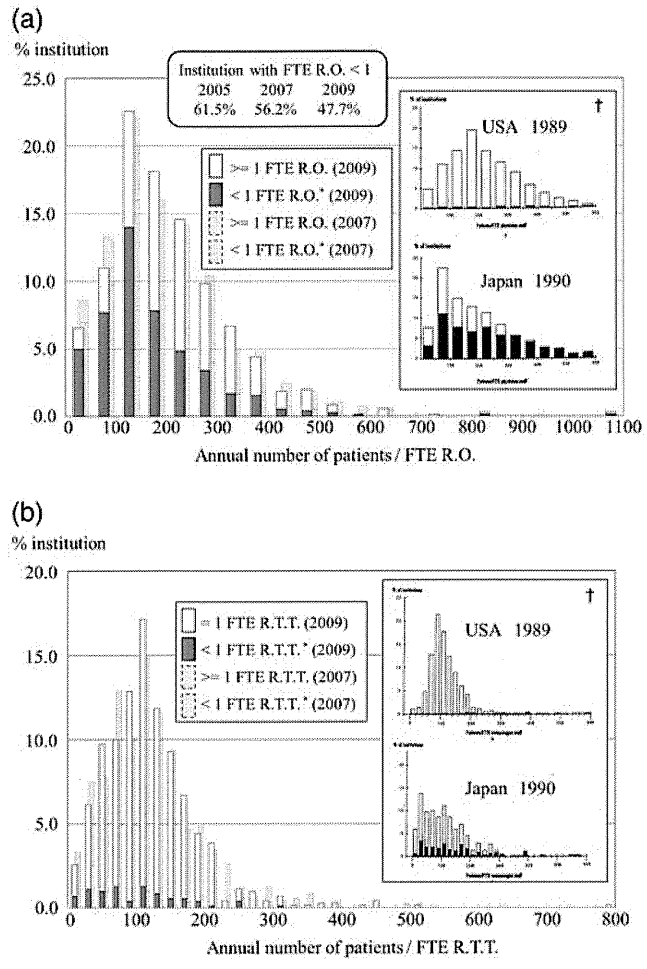

Fig. 1. (**a**) Percentage distribution by institution for patient load/full-time equivalent (FTE) radiation oncologists (ROs) in Japan; (**b**) corresponding percentage distribution for patient load/full-time equivalent (FTE) radiotherapy technologists in Japan (a) Spacing of the bars represents intervals of 50 patients/FTE radiation oncologist. Open bars represent institutions with one or more FTE staff member, and solid bars represent institutions with less than one FTE radiation oncologist. The number of FTEs for institutions with less than one FTE staff member was calculated as the equivalent of one FTE to avoid overestimating patient load per FTE RO or staff. (b) *Spacing of the bars represents intervals of 20 patients/FTE staff. †Corresponding data for the USA and Japan are shown for reference [3]. Originally published in Int. J. Radiat. Oncol. Biol. Phys. 34(1): 235–242.

metastasis ranged from 10.4% for A2 to 15.7% for B2. Overall, more patients with bone metastasis were treated with radiation at non-academic than at academic institutions. The number of patients with brain metastasis decreased slightly by –4.7% compared with 2007 [6].

Geographic patterns

Figure 3 shows the geographic distributions for 47 prefectures of the annual number of patients (new plus repeat) per 1000 population arranged in increasing order of the number of JASTRO-certified ROs per 1 000 000 population [20]. There were significant differences in the use of RT, from 1.1 patients per 1000 population (Saitama) to 2.3 (Tokyo). The average number of cancer patients per 1000 population per quarter ranged from 1.57 to 1.80 ($P = 0.1585$). The more JASTRO-certified physicians there were in a given area, the more RT tended to be used for cancer patients, although the correlation was of borderline significance. Similar trends were clearly observed in 2005 [5] and 2007 [6]. Compared with 2005 and 2007, the utilization rate of RT increased in every prefecture in 2009. However, the rates in 2007 and 2009 were not related to prefectural population density as was also observed in the data for 1990 [3].

DISCUSSION

In 1990, there were fewer facilities for radiation treatment and fewer patients treated with radiation in Japan than in the USA. Over the next 19 years, however, the number of patients in Japan increased significantly by a factor of 3.2 [3]. On the other hand, the utilization rate of radiation for new cancer patients remained at 27.6%, less than half that recorded in the USA and European countries, although the rate increased slightly by 0.75% per year between 2007 [6] and 2009. For implementation of the Cancer Control Act, comparative data of the structure of radiation oncology in Japan and in the USA as well as relevant PCS data proved to be very helpful.

Compared with 1990, the number of Linac systems increased significantly by a factor of 2.62 and increased by 1.1% over 2007 [6], while the number of systems using telecobalt decreased to only nine and remained stable. Furthermore, the use of various functions of Linac, such as dual energy, 3DCRT (MLC width <1 cm) and IMRT, improved significantly. The number of high dose rate (HDR) RALS in use has increased and ^{60}Co RALS has been largely replaced with ^{192}Ir RALS. In 2009, CT simulators had been installed in 82.1% of institutions throughout the country for a 15.7% increase over 2007 [6] and exceeded the number of X-ray simulators (51.6%). Radiotherapy planning systems (RTPs) were used at 96.0% of institutions for an increase in the number of RTPs of 6.59 times compared with 1990 [3]. Maturity of the functions of Linac and installation rates of CT simulators and systems using ^{192} Ir RALS also improved further compared with 2007 [6], but were still closely correlated with the PCS institutional stratification, which could therefore aid accurate differentiation between structural maturity and immaturity and the identification of structural targets for improvement.

The staffing patterns in Japan also improved in terms of numbers. However, institutions with less than one FTE radiation oncologist on their staff still account for 47.7% nationwide, although this represents an 8% decrease

Table 5. Primary sites of cancer treatment with RT in 2009 by PCS institutional stratification for new patients

Primary site	A1 ($n = 69$)		Comparison with data of 2007[a] (%)	A2 ($n = 66$)		Comparison with data of 2007[a] (%)	B1 ($n = 256$)		Comparison with data of 2007[a] (%)	B2 ($n = 253$)		Comparison with data of 2007[a] (%)	Total ($n = 644$)		Comparison with data of 2007[a] (%)
	n	%		*n*	%		*n*	%		*n*	%		*n*	%	
Cerebrospinal	1906	3.8	−5.7	994	5.4	38.1	4812	6.2	−13.6	1349	5.4	−3.4	9061	5.3	−6.6
Head and neck (including thyroid)	6444	12.8	−1.2	2500	13.6	17.7	7601	9.8	21.4	1560	6.3	−5.7	18 105	10.6	9.3
Esophagus	3247	6.5	−5.8	1196	6.5	1.4	3735	4.8	−8.2	1416	5.7	−3.9	9594	5.6	−5.7
Lung, trachea and mediastinum	7880	15.7	5.6	2771	15.0	−2.8	15 855	20.4	−5.7	5801	23.3	−0.7	32 307	18.9	−2.0
Lung	7335	14.6	8.0	2438	13.2	−0.6	14 358	18.5	−1.3	5060	20.4	−6.2	29 191	17.0	0.0
Breast	10 869	21.7	5.2	3637	19.7	−0.7	19 373	24.9	11.8	5955	24.0	18.8	39 834	23.3	9.6
Liver, biliary tract, pancreas	1948	3.9	1.0	806	4.4	19.6	2907	3.7	3.6	980	3.9	−4.2	6641	3.9	3.2
Gastric, small intestine, colorectal	2167	4.3	4.4	945	5.1	−6.9	3783	4.9	−6.2	1384	5.6	−7.6	8279	4.8	−4.0
Gynecologic	3430	6.8	3.5	1135	6.2	7.3	2914	3.7	−4.7	737	3.0	−5.6	8216	4.8	0.0
Urogenital	7167	14.3	5.8	2470	13.4	−1.1	10 019	12.9	2.8	3394	13.7	13.4	23 050	13.5	4.7
Prostate	5926	11.8	9.9	1888	10.2	8.0	7618	9.8	8.6	2487	10.0	20.3	17 919	10.5	10.4
Hematopoietic and lymphatic	2639	5.3	1.9	963	5.2	7.0	3264	4.2	−10.1	1083	4.4	15.8	7949	4.6	−1.3
Skin, bone and soft tissue	1269	2.5	−12.8	496	2.7	2.5	1590	2.0	−15.4	738	3.0	−1.7	4093	2.4	−10.4
Other (malignant)	541	1.1	−39.5	241	1.3	1.7	852	1.1	−5.0	307	1.2	5.1	1941	1.1	−16.3
Benign tumors	675	1.3	−31.7	278	1.5	4.5	1112	1.4	−13.7	155	0.6	−16.7	2220	1.3	−18.6
Pediatric <15 y (included in totals above)	461	0.9	4.8	145	0.8	25.0	349	0.4	−6.7	137	0.6	8.7	1092	0.6	3.4
Total	50 182	100	0.8	18 432	100	4.3	77 817	100	0.6	24 859	100.0	4.3	171 290	100	1.5

Abbreviations as in Table 2.

[a]Rate of increase compared with the data of 2007. Calculating formula: $\frac{data\ of\ 2009\ (n) - data\ of\ 2007\ (n)}{data\ of\ 2007\ (n)} \times 100\ (\%)$

[b]Total number of new patients different with these data, because no data on primary sites were reported by some institutions.

Table 6: Distribution of specific treatments and numbers of patients treated with these modalities by PCS stratification of institutions

Specific therapy	A1 ($n = 70$)		A2 ($n = 70$)		B1 ($n = 280$)		B2 ($n = 280$)		Total ($n = 700$)		Comparison with data of 2007[a] (%)
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Intracavitary RT											
Treatment facilities	64	91.4	28	40.0	58	20.7	1	0.4	151	21.6	
Cases	1864		421		848		6		3139		–3.0
Interstitial RT											
Treatment facilities	55	78.6	20	28.6	32	11.4	2	0.7	109	15.6	
Cases	2482		550		993		45		4070		23.3
Radioactive iodine therapy for prostate											
Treatment facilities	50	71.4	16	22.9	29	10.4	1	0.4	96	13.7	
Cases	1842		360		856		22		3080		14.5
Total body RT											
Treatment facilities	63	90.0	31	44.3	65	23.2	21	7.5	180	25.7	
Cases	798		235		620		137		1790		4.9
Intraoperative RT											
Treatment facilities	15	21.4	6	8.6	4	1.4	3	1.1	28	4.0	
Cases	135		21		9		8		173		–31.1
Stereotactic brain RT											
Treatment facilities	43	61.4	26	37.1	94	33.6	39	13.9	202	25.8	
Cases	1660		658		9671		1866		13 855		10.4
Stereotactic body RT											
Treatment facilities	51	72.9	26	37.1	71	25.4	17	6.1	165	23.6	
Cases	1087		185		1125		140		2537		1.9
IMRT											
Treatment facilities	47	67.1	10	14.3	36	12.9	8	2.9	101	14.4	
Cases	1855		94		1961		386		4296		34.8
Thermoradiotherapy											
Treatment facilities	7	10.0	5	7.1	4	1.4	4	1.4	20	2.9	
Cases	185		38		137		31		391		15.0

PCS = Patterns of Care Study; RT = radiotherapy; IMRT = intensity-modulated radiotherapy.

[a]Rate of increase compared with the data of 2007. Calculating formula: $\frac{data\ of\ 2009\ (n) - data\ of\ 2007\ (n)}{data\ of\ 2007\ (n)} \times 100\ (\%)$

compared with 2007 [6]. In other words, nearly half the institutions in Japan still rely on part-time radiation oncologists. There are two reasons for this. First, although the number of FTE radiation oncologists grew by 13.7 % over the last 2 years, the number of cancer patients who require radiation has also increased by 10% over the same period. Second, specialist fees for radiation oncologists in academic institutions are not covered by the Japanese medical care insurance system, which is strictly controlled by the government. Therefore, most radiation or other oncologists at academic institutions must work part-time at affiliated hospitals in the B1 and B2 groups to earn a living. To reduce the number of institutions that rely on part-time radiation oncologists and thus may encounter problems with their quality of care, a reform of Japan's current medical care system based on treatment outcome is required, especially as it applies to staff at academic institutions. However, great care is needed to ensure that the long-term success of radiation oncology in Japan and patient benefits are well balanced with costs. For this reason, personal identification of ROs in both A and B institutions was included and recorded in the 2007 and 2009 surveys for further detailed analysis of patient load and real cost [7]. There were significant differences in the average practice index for patients between ROs working mainly in main university hospitals and in affiliated hospitals (1.07 vs 0.71: $P < 0.0001$). Under the current Japanese national medical system, patterns of work by ROs at academic facilities appear to be problematic for fostering true specialization of ROs. On the other hand, according to the increase in the number of cancer patients who require RT, B1 institutions are gradually offering full-time positions for ROs. However, the speed of offers for second or third positions are slow in individual institutions due to tight budgets in most B1 institutions. Therefore, monitoring these structural data is necessary to convince local government to improve working environments for ROs. Even under these conditions, however, the number of FTE ROs increased by 2.57 times compared with 1990 [3], and by 13.7% over 2007 [6]. On the other hand, patient load per FTE RO also increased by 1.35 times to 231.9 during the same period 1990–2009, but registered a –0.67% decrease compared

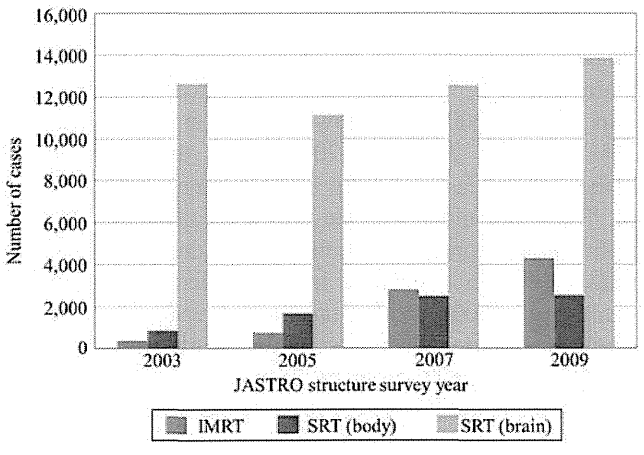

Fig. 2. Trends in numbers of patients treated with SRT for brain, SRT for body and IMRT by survey year

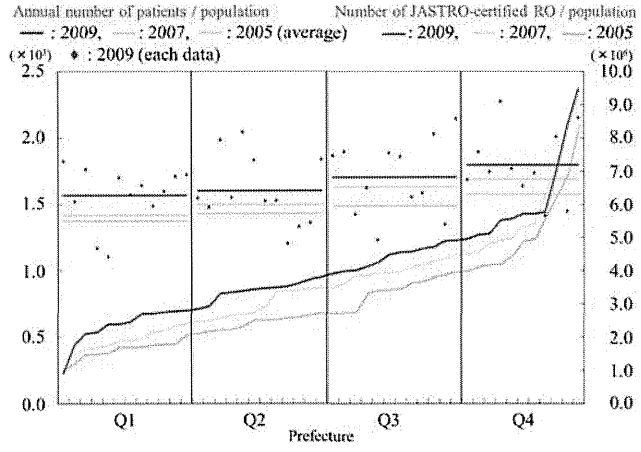

Fig. 3. Geographic distribution for 47 prefectures of annual numbers of patients (new plus repeat) per 1000 population in increasing order for JASTRO-certified radiation oncologists (RO)/ 1 000 000 population by prefecture Q1, 0–25%; Q2, 26–50%; Q3, 51–75%; and Q4, 76–100%. Horizontal lines show average annual number of patients (new plus repeat) per 1000 prefectural population per quarter.

Table 7: brain metastasis or bone metastasis patients treated with RT in 2007 by PCS institutional stratification

Metastasis	Patients										Comparison with data of 2007[a] (%)
	A1 ($n = 70$)		A2 ($n = 70$)		B1 ($n = 280$)		B2 ($n = 280$)		Total ($n = 700$)		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Brain	3534	5.2	1363	6.0	12 394	12.2	3043	9.7	20 334	9.3	–4.3
Bone	6948	11.2	2419	10.6	12 618	12.4	4921	15.7	26 906	12.4	–3.8

Data presented as number of patients, with percentages in parentheses.
[a]Rate of increase compared with the data of 2007. Calculating formula: $\frac{data\ of\ 2009\ (n) - data\ of\ 2007\ (n)}{data\ of\ 2007\ (n)} \times 100\ (\%)$

with 2007 [6]. This may reflect the growing popularity of RT due to an increase in the elderly population and recent advances in technology and improvement in clinical results. The caseload ratio in Japan has therefore already exceeded the limit of the Blue Book guidelines of 200 patients per radiation oncologist and improved only slightly in 2009 [21, 22]. The percentage distribution of institutions by patient load per RO showed a slightly high percentage for smaller patient load/RO than that in the USA in 1989 [3], but also showed a major shift to a larger size in 2009 compared with 1990. In Japan, the patterns are now becoming similar to those of the USA in 1989 [3], indicating that Japanese radiation oncology is catching up quickly with western systems and growing steadily in spite of limited resources. Furthermore, additional recruiting and education of ROs continue to be top priorities for JASTRO. The distribution of patient load per RT technologist shows that only 17.3% of institutions met the narrow guideline range (100–120 patient per RT technologist) and the rest showed a dense distribution around the peak level. Compared with the distribution in the USA in 1989, nearly 18% of institutions in Japan had a relatively low caseload of 10–60, because there are still a large number of smaller B2-type institutions, which account for nearly 40% of institutions that do not attain the range specified by the guidelines. As for medical physicists, an analysis of patient load for FTE staff similar to that for RT technologists remains difficult, because the number of the former was very small and they were working mainly in metropolitan areas. However, RT technologists in Japan have been acting partly as medical physicists. Their training duration has changed from 3 to 4 years over the last decade, and graduate and postgraduate courses have been introduced. Currently, RT technologists who have obtained a master's degree or those with enough clinical experience can take the examination for qualification as a medical physicist, as can those with a master's degree in science or engineering like in the USA or Europe. A unique, hybrid education system for medical physicists has thus been developed in Japan since the Cancer Control Act actively started to support improvement in quality assurance and quality control (QA/QC) specialization for RT. However, the validity of this education and training system remains to be proven, not only for QA/QC but also for unique research and developmental activities. The discrepancy between FTE medical physicists and the number of registered medical physicists in Japan reflects the fact that their role in the clinic is not recognized as a full-time position only for medical physics services.

Analysis of the distribution of primary sites for RT showed that the number of lung cancer patients at A1-type institutions increased by 8% compared with 2007. On the other hand, more head and neck cancer patients were treated at A1-, A2- or B1-type institutions, but the rates of increase compared with 2007 were high for A2 and B1 institutions. The increase in the number of lung cancer patients at A1 institutions in 2009 was noteworthy and the same goes for that of prostate cancer patients or breast cancer patients at A1-, A2-, B1- and B2-type institutions. This suggests that stereotactic body RT (SBRT) for lung cancer at A1 and 3DCRT for prostate cancer or breast-conserving therapy for breast cancer (BCT) at A1, A2, B1 and B2 were used more frequently in 2009. Especially in B2-type institutions, breast cancer patients (18.8%) and prostate cancer patients (20.3%) increased at two of the highest rates. This indicates that treatments such as 3DCRT and BCT were disseminated widely to B2-type institutions as a standard. The number of patients with brain or bone metastasis did not increase compared with 2007 [6]. The use of specific treatments and the number of patients treated with these modalities were significantly affected by institutional stratification, with more specific treatments being performed at academic institutions. These findings indicate that significant differences in patterns of care, as reflected in structure, process and possibly outcome for cancer patients continued to be prevalent in Japan in 2009. However, these differences point to opportunities for improvement. The Japanese PCS group published structural guidelines based on PCS data [22] and we are using the structural data obtained in 2009 to revise the Japanese structural guidelines for radiation oncology in the near future. The use of intraoperative RT decreased significantly from 2005 to 2007 and showed a similar rate of decrease (35%) between 2007 and 2009, while that of thermoradiotherapy increased slightly by 15% compared with 2007 [6]. These two modalities are thus not considered mainstay treatments in Japan. The numbers of patients with bone metastasis or brain metastasis in 2009 decreased, compared with those in 2007. Within the limited resources of departments of radiation oncology, more efforts may be made, focusing on radical treatment than palliative ones. Also general treatments such as bisphosphonates or narcotic drugs such as opioids for bone metastasis may relatively reduce the candidates for RT. The reason for the reduction in use of RT for brain metastasis is unknown.

Geographic patterns showed that there were significant differences among prefectures in the use of RT, and the number of JASTRO-certified physicians per population was associated with the utilization of RT in 2005 [5], 2007 [6] and 2009, so that a shortage of radiation oncologists or medical physicists on a regional basis will remain a major concern in Japan. Compared with 2005 [5] and 2007 [6], however, the utilization rate of radiation for new cancer patients in 2009 showed further increase. JASTRO has been making every effort to recruit and educate radiation oncologists and medical physicists through public relations, to establish and conduct training courses at academic

institutions, to become involved in the national examination for physicians and to seek an increase in the coverage of fees for ROs by the government-controlled insurance scheme.

In conclusion, the Japanese structure of radiation oncology has clearly and steadily improved over the past 19 years in terms of installation and use of equipment and its functions, but shortages of man power and differences in maturity depending on type of institution and caseload remain. Structural immaturity is an immediate target for improvement, while for improvements in process and outcome, the PCS or National Cancer Database (NCDB), which are currently operational and the subject of close examination, can be expected to perform an important function in the future of radiation oncology in Japan.

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Review

High dose rate brachytherapy for oral cancer

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Brachytherapy results in better dose distribution compared with other treatments because of steep dose reduction in the surrounding normal tissues. Excellent local control rates and acceptable side effects have been demonstrated with brachytherapy as a sole treatment modality, a postoperative method, and a method of reirradiation. Low-dose-rate (LDR) brachytherapy has been employed worldwide for its superior outcome. With the advent of technology, high-dose-rate (HDR) brachytherapy has enabled health care providers to avoid radiation exposure. This therapy has been used for treating many types of cancer such as gynecological cancer, breast cancer, and prostate cancer. However, LDR and pulsed-dose-rate interstitial brachytherapies have been mainstays for head and neck cancer. HDR brachytherapy has not become widely used in the radiotherapy community for treating head and neck cancer because of lack of experience and biological concerns. On the other hand, because HDR brachytherapy is less time-consuming, treatment can occasionally be administered on an outpatient basis. For the convenience and safety of patients and medical staff, HDR brachytherapy should be explored. To enhance the role of this therapy in treatment of head and neck lesions, we have reviewed its outcomes with oral cancer, including Phase I/II to Phase III studies, evaluating this technique in terms of safety and efficacy. In particular, our studies have shown that superficial tumors can be treated using a non-invasive mold technique on an outpatient basis without adverse reactions. The next generation of image-guided brachytherapy using HDR has been discussed. In conclusion, although concrete evidence is yet to be produced with a sophisticated study in a reproducible manner, HDR brachytherapy remains an important option for treatment of oral cancer.

Keywords: brachytherapy; oral cancer; high dose rate

INTRODUCTION

Because adjacent normal tissues, such as the salivary glands, mandible, and mastication muscles, are at risk of damage during treatment with external beam radiation therapy (EBRT), brachytherapy is an important alternative to conventional radiotherapy. Brachytherapy provides a high localized dose of radiation, with rapid fall-off and short overall treatment time [1]. It can be applied as a sole treatment, as a treatment complementary to surgery, and as a local boost in combination with EBRT.

Low-dose-rate (LDR) brachytherapy has been employed in the treatment of carcinoma of the lip, tongue, floor of the mouth, oral mucosa, base of the tongue, tonsillar region, soft palate, and nasopharynx, and has been the gold standard for brachytherapy. With the advent of new

technologies, high-dose-rate (HDR) and pulsed-dose-rate (PDR) brachytherapy have been adapted in many institutes to avoid exposure of health care providers to radiation. HDR and PDR stepping source technology offer the advantage of optimizing dose distribution by varying dwell times [1]. The application of HDR brachytherapy has expanded to many sites, having been used in treatment of gynecological cancer, breast cancer, and prostate cancer [2, 3]. Guedea *et al.* reported that gynecological brachytherapy remains the most common application, although the use of brachytherapy in prostate cancer and breast cancer has increased in Europe [4].

CT-based dosimetry has become increasingly common since 2002. Use of HDR and PDR techniques has increased markedly, while use of both LDR and medium-dose-rate brachytherapy has declined. However, for head and neck cancer, HDR usage decreased in Group I institutes (those in countries with the highest GDP) from 5% (2002) to 2% (2007) [4]. LDR and PDR interstitial brachytherapies (ISBT) were utilized instead. Accordingly, HDR brachytherapy has not become widely used in the radiotherapy community for treating head and neck cancer because of lack of experience and biological concerns [5, 6].

Mazeron *et al.* noted that the efficacy and safety of HDR brachytherapy must be validated in prospective studies. If it is the only technique available, treatment should be delivered in fractions of <3–4 Gy, according to GEC-ESTRO recommendations [1]. Several members of the American Brachytherapy Society expressed concern about potential morbidity with fraction sizes as large as 6 Gy to the oral cavity [6]. On the other hand, very little clinical evidence has been found suggesting a higher risk of high-dose fractionation (≥6 Gy). Acceptable results have been obtained from a few institutes.

To enhance the role of HDR brachytherapy, we reviewed the results of HDR brachytherapy, including our experiences in Phase I/II and III trials, to investigate the next generation of image-guided brachytherapy using HDR.

HDR brachytherapy for tongue cancer

Tongue cancer located anterior to the circumvallate papillae vitally affects not only speech, but also coordination of chewing and swallowing. Because radiation therapy is considered to be a minimally invasive treatment procedure, it has the advantage of preserving the shape and functions of the tongue. Brachytherapy alone is recommended for T1N0 and T2N0 tumors <4 cm. For tumors >3–4 cm or N1 lesions, although surgery is often preferred, brachytherapy can be delivered as a boost after 40–45 Gy of EBRT to the neck and oral cavity. In general, the local control rate is higher than 90% for T1 and T2N0 tumors treated with LDR brachytherapy alone [1]. The local control rate is lower in patients with larger tumors treated with EBRT and a brachytherapy boost. Approximately 10–30% of patients may develop soft tissue necrosis within the implant volume. Osteoradionecrosis may occur in 5–10% of cases. The vast majority of necroses heal spontaneously after medical treatment. Surgical intervention is necessary in only 1–2% of patients [1].

Lau *et al.* initiated a Phase I/II protocol using HDR-ISBT [7] (Table 1). In that study, 27 patients were treated (Tl, $n = 10$; T2, $n = 15$; and T3, $n = 2$). Seven fractions × 6.5 Gy of HDR-ISBT were administered twice-daily, with a minimum interval time of 6 h over a period of 3.5 days. The actual tumor control probability after HDR brachytherapy was 53% at 5 years. Local control rates for Tl and T2 tumors were lower than those for comparable historical controls treated at our institution using LDR radium (Ra-226) or cesium (Cs-137) needle implants and iridium (Ir-192) wire implants. In addition, a trend was observed toward a higher incidence of severe complications for HDR patients compared with the historical controls treated with LDR brachytherapy.

On the other hand, Leung *et al.* reported good outcomes for eight patients treated solely with HDR-ISBT. Five patients had TlN0 disease, and the remaining three had T2N0 disease [8]. The median follow-up period for these patients was 26 months. The median dose administered was 60 Gy/10 fractions over 6 days. Mandibular and maxillary shields were inserted prior to treatment. Mucositis for 6–20 weeks (median, 10 weeks) was observed in all patients. No local failure was evident after the median follow-up period. One patient treated with a double planar implant developed Grade 3 necrosis of the soft tissue and bone. Leung *et al.* [8] concluded that the HDR remote after-loading technique is useful because it provides a local control rate of 100% with acceptable morbidity. On further investigation in 2002, they found that a protocol of 5.5 Gy/10 fractions was feasible, resulting in a local control rate of 94% at 4 years in ten T1 and nine T2 patients without severe morbidity [9].

Ohga *et al.* treated 28 patients with N0 oral tongue cancer using HDR-ISBT combined with local injection of bleomycin [10]. A median dose of 5 mg bleomycin was injected locally, and 16–20 Gy was delivered to the area surrounding the applicators within the first two days for control of the tumor implant. The 2-year local recurrence-free survival rate in that study was 96% [T1/2: 100% (8/8, 15/15); T3: 80% (4/5)]. The minimum tumor dose was decreased step-by-step. Local recurrence rates of 12.5% (1/8), 0% (0/14), and 0% (0/6) were observed in patients with median minimum tumor doses of 60, 50 and 40 Gy, respectively. Local recurrence rates did not increase when the minimum tumor dose decreased. Late adverse effects included the following: tongue ulcer (11%, 3/28), oral floor ulcer (4%, 1/28), and osteonecrosis (4%, 1/28). These results suggest that decrease in the minimum tumor dose to <60 Gy may be possible in combination treatment with local injection of bleomycin.

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

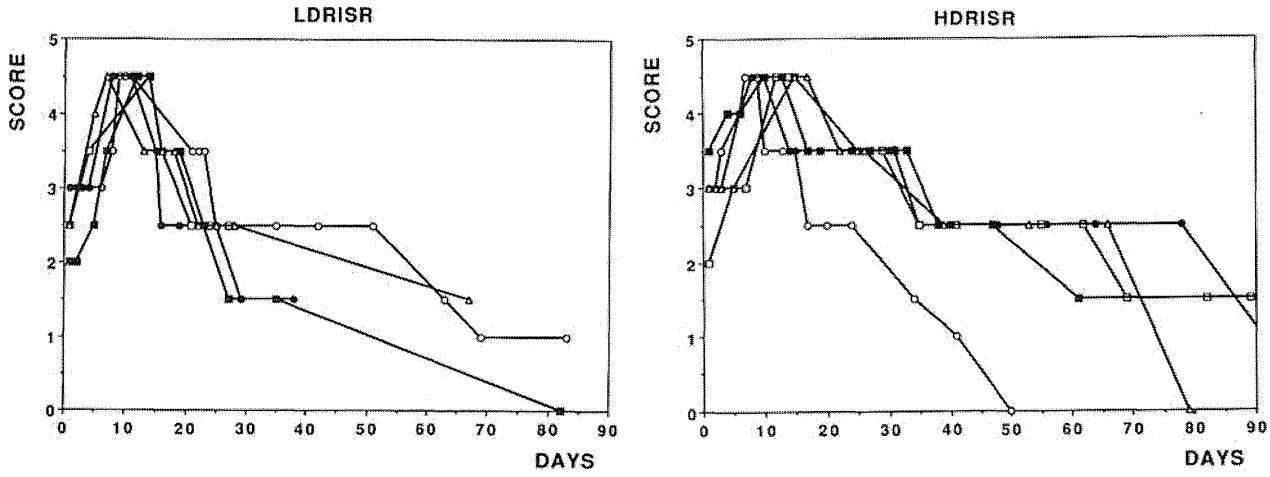

Fig. 1. Time course of mucosal reactions as observed after LDR or HDR interstitial brachytherapy for mobile tongue cancer [19].

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

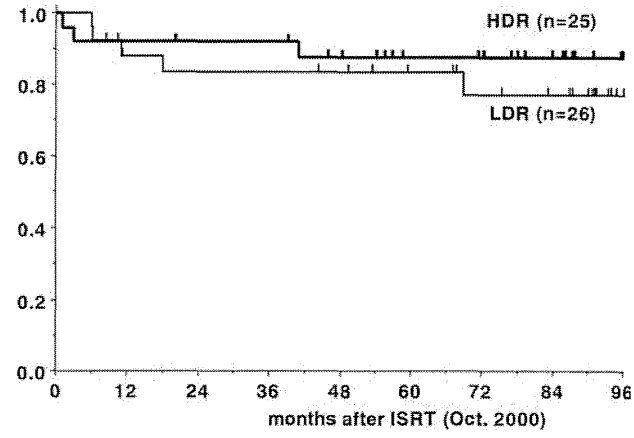

Fig. 2. Comparison of local control between HDR and LDR in Phase III study [21].

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