

Reirradiation using robotic image-guided stereotactic radiotherapy of recurrent head and neck cancer

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ABSTRACT

The purpose of this study was to examine the prognosis for patients with head and neck cancer after reirradiation using Cyberknife stereotactic body irradiation with special focus on mucosal ulceration. We conducted a retrospective multi-institutional review of 107 patients with previously irradiated head and neck cancer. The median follow-up time for all patients was 15 months, and the 2-year overall survival rate was 35%. Significant prognostic factors for overall survival were primary site (nasopharynx versus other sites), presence of ulceration, and PTV volume. Detailed analysis of ulceration showed a lower response rate (28%) in the ulceration (+) group than the ulceration (–) group (63%; $P = 0.0045$). The 2-year overall survival rates were 8% in the ulceration (+) group and 42.7% ($P = 0.0001$) in the ulceration (–) group, respectively. We recorded 22 severe toxicities, including 11 patients with carotid blow-out syndrome (CBOS), which was fatal in 9 patients. CBOS occurred in 6 patients with ulceration (6/25; 24%), and 5 patients experienced CBOS without ulceration (5/82; 6%; $P = 0.027$). In conclusion, ulceration is an important prognostic factor, not only for adverse events but also for survival after reirradiation using CyberKnife.

KEYWORDS: head and neck cancer, reirradiation, stereotactic radiotherapy, ulceration

INTRODUCTION

Several advanced treatments have been developed in recent years aimed at improving head and neck cancer outcomes, including stereotactic body irradiation (SBRT), intensity-modulated radiotherapy, and chemoradiotherapy (e.g. cisplatin and/or cetuximab) [1]. However, locoregional failure occurs in 20–30% of patients and represents a main treatment obstacle [2, 3]. With a median survival rate of 6–10 months, chemotherapy is the mainstay treatment in patients with locoregional failure, but only 20–30% of patients are candidates for salvage surgery [3, 4]. Reirradiation has become a potentially curative therapy with the

advent of modern radiotherapy techniques, such as intensity-modulated radiotherapy and SBRT [5]. CyberKnife is a nearly real-time image-guided SBRT system suitable for precise dose delivery over short treatment periods. Therefore, it is used in reirradiation for head and neck cancer [6–9].

Short-period SBRT using hypofractionation has been studied because of its precise dose delivery with limited acute toxicity that enables the use of salvage radiotherapy even in frail patients. We previously reported positive initial responses to SBRT [6]; however, this study was limited because it involved a small number of patients

treated at a single institute. Furthermore, lethal toxicity [i.e. carotid-blow out syndrome (CBOS)] was identified as a serious consequence [10]. We found that the presence of mucosal ulceration was a risk factor for CBOS, particularly in patients where tumor invasion of the carotid artery was $>180^\circ$ [11]. Those results prompted us to examine the role of ulceration because it could also be a potentially important tumor characteristic for prognosis as well as toxicity. The aim of this study was to examine prognostic factors after reirradiation using CyberKnife, particularly focusing on ulceration.

MATERIALS AND METHODS

We included patients with recurrent head and neck tumors treated at the Soseikai General, Fujimoto Hayasuzu, Okayama Kyokuto, and Osaka University Hospitals (Japan) between 2000 and 2010. All recurrences occurred in an area previously irradiated with ≥ 40 Gy. We excluded patients who received SBRT as a planned boost after

conventional external radiotherapy and those with other disease sites outside the reirradiation area. The first course of radiotherapy was delivered by a conventional technique using either Linac curative intent or postoperative radiotherapy. The median age of patients was 63 years (range, 35–88 years) and they included 78 males and 29 females. Patient and disease characteristics are listed in Table 1.

The most common primary sites were the nasopharynx (38%), oropharynx (19%) and nasal passage/sinus (18%). SBRT reirradiation was performed using the CyberKnife system. Patients were treated with a median dose of 30 Gy (range, 15–39 Gy) in a median of five fractions (range, 3–8 fractions) prescribed as D90, D95, or a marginal dose. D90 and D95 doses were defined by a minimum dose covering 90% and 95%, respectively, of the planning target volume (PTV). Most frequently used doses were 27 Gy ($n = 33$), 30 Gy ($n = 21$), 35 Gy ($n = 14$), 25 Gy ($n = 9$), and 37 Gy ($n = 7$) in five fractions, among others. The marginal dose was defined as the percentage (100% = maximum dose) of an

Table 1. Characteristics and treatment factors of patients with CyberKnife reirradiation

Variables	Strata	Median (range) or No. ($n = 107$)	(%)
Age		63 (35–88)	
Gender	Female	29	(27)
	Male	78	(73)
Primary site	Nasopharynx	41	(38)
	Oropharynx	21	(19)
	Hypopharynx	11	(10)
	Oral	14	(13)
	Nasal & sinus	20	(18)
Location	Primary	79	(72)
	Lymph node	11	(10)
	Primary & lymph node	17	(16)
Surgical history	No	60	(55)
	Yes	47	(43)
Ulceration	No	82	(75)
	Yes	25	(23)
Planning target volume	(cm^3)	28.4 (1–339)	
Interval	(months)	14.5 (0.7–1180)	
Prescribed dose	(Gy)	30 (15–39)	
Number of fractions		5 (3–8)	
EQD2	[Gy ($\alpha/\beta = 10$)]	40 (18.75–74.75)	
Previous prescribed dose	(Gy)	60 (40–116)	
Previous no. of fractions		30 (20–62)	
Cumulative EQD2	[Gy ($\alpha/\beta = 10$)]	101 (66.4–150)	

EQD2 = the biologically equivalent dose calculated into equivalent 2-Gy fractions.

isodose curve covering the PTV. Ulceration (mucosal ulceration in the tumor lesion) was identified by visual inspection, including fiberoptic, contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). Dose constraints to the critical organs were defined while taking into account the previously delivered dose. No patient received concurrent chemotherapy. Following the completion of treatment, radiological evaluations consisting of a CT and/or an MRI were performed along with an evaluation of tumor response using the Response Evaluation Criteria in Solid Tumors system. In principle, follow-up by physical examination was performed at least in 1-month intervals for the first year and at 3–6-month intervals thereafter. Examination with imaging procedures, such as CT, MRI and/or ultrasonography, were performed after 3 months, 6 months, 1 year, 1.5 years, and 2 years and at 1-year intervals thereafter or when local or lymph node recurrence was suspected. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria scale version 3.0. The biologically equivalent dose was calculated as equivalent 2-Gy fractions (EQD2) using a linear–quadratic model, where $\alpha/\beta = 10$ for tumors and $\alpha/\beta = 3$ for organs at risk.

$$\text{EQD2} = (\text{prescribed dose} [\times \alpha/\beta + \text{dose per fraction}]) / (\alpha/\beta + 2)$$

We divided EQD2 by >40 Gy (EQD2) [= 30 Gy/5 fractions] or less as a median value.

Statistical analysis

All statistical analyses were performed using Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). Percentages were analyzed using the χ^2 test, and values were compared using the Mann–Whitney U test. The durations of survival were calculated from the first day of CyberKnife SBRT. Complications were graded using the Common Terminology Criteria for Adverse Events version 3.0. Actuarial survival curves were generated using the Kaplan–Meier method, and comparisons were made using the log-rank test. Variables that had *P*-values <0.10 were tested further by multivariate analysis using a Cox proportional hazards model. All analyses used the *P* < 0.05 level of significance unless otherwise indicated.

RESULTS

Ulceration was more commonly observed in oral (43%) and oropharyngeal cancers (52%) compared with other types [nasopharynx (17%), hypopharynx (9%), nasal/paranasal (0%); *P* = 0.0003; Supplemental Table 1]. The ulceration (+) group showed a median PTV volume of 41.9 cm³, and 61% of patients (50/82) had a surgical history. The ulceration (–) group had a PTV volume of 27.0 cm³ (*P* = 0.06), and 40% of patients (10/25) had a surgical history (*P* = 0.06). Therefore, we concluded that larger tumors have a higher probability of developing ulceration postoperatively.

The initial response rate [complete response (CR) + partial response (PR)] was 54%, with a CR seen in 23 patients and PR in 35. Stable disease was observed in 39 patients and progressive disease in 9 (initial tumor response could not be assessed in 1 patient because of poor general condition). The ulceration (+) group showed a lower response rate (28%: 1 CR + 6 PR = 7/25) than the ulceration (–) group (63%: 22 CR + 29 PR = 51/81; *P* = 0.0045). Locoregional failure was observed in 35 patients (33%) as initial tumor progression. The locoregional control rate for all patients at 2 years was 64% [95% confidence interval (CI), 53–74%]. Univariate analysis revealed primary tumor site (nasopharynx versus other sites) (*P* = 0.02), and

the presence of ulceration (*P* = 0.01) were statistically significant predictors of locoregional control rate.

The median survival time was 14.4 months (95% CI, 10.8–19.4 months), with a median follow-up of 15 months (10–122 months). The 1- and 2-year overall survival (OS) rates were 55% (95% CI,

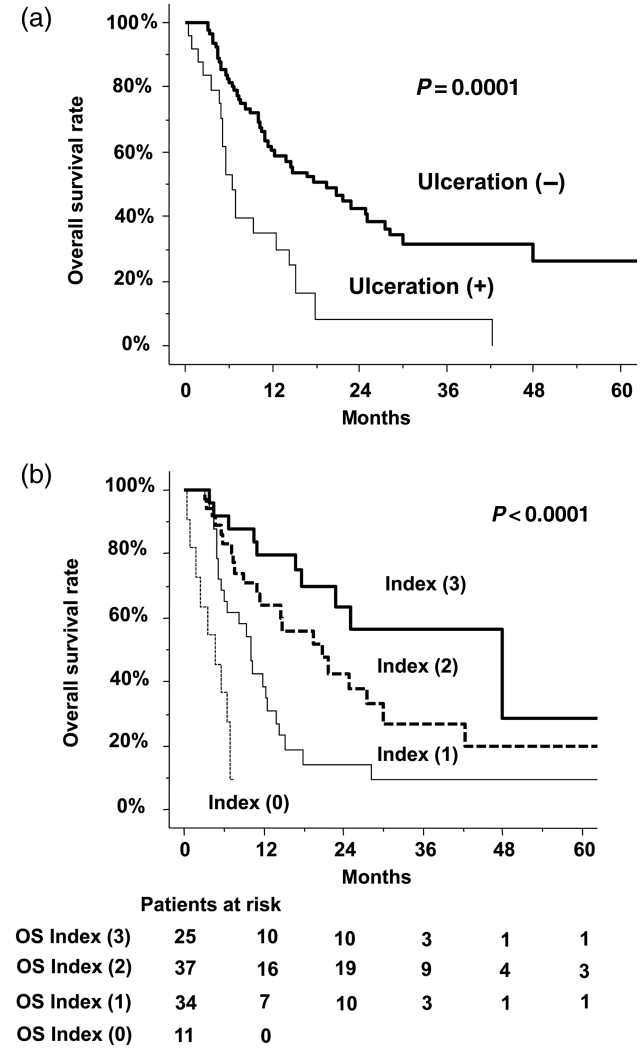


Fig. 1. Overall survival rate (OS). (a) Overall survival rate according to ulceration. The thick line depicts the outcome for patients with absence of ulceration and the thin line depicts the outcome for patients with presence of ulceration. (b) Overall survival rates are stratified by prognostic index. By using three statistically significant prognostic factors, we made a prognostic index = [summation of those three factors classified as 0 or 1: primary site nasopharynx (1) or not (0), PTV < 40 cm³ (1) or not (0), absence of ulceration (1) or not (0)]. The 2-year survival rates were not available for Index 0 (*n* = 14; 9% at 7.6 months), 14% (95% CI, 0.01–28%) for Index 1 (*n* = 32), 43% (95% CI, 24–62%) for Index 2 (*n* = 38) and 64% (95% CI, 43–84%) for Index 3 (*n* = 25) (*P* < 0.0001). This risk classification system was able to separate the risk group well.

45.6–65.3%) and 35% (95% CI, 25.5–46.1%), respectively. The 2-year OS rates were 8% in the ulceration (+) group and 42.7% in the ulceration (–) group, respectively (Fig. 1a). Univariate analysis revealed that primary site (nasopharynx), small PTV volume, absence of ulceration, higher prescribed dose (EQD2 \geq 40 Gy = 30 Gy/5 fractions) and long radiotherapy interval were favorable predictive factors for OS (Table 2). Multivariate analysis revealed that primary site, absence of ulceration, and small PTV volume were statistically significant predictors for OS (Table 3).

To investigate the value of considering ulceration in prognosis, we performed an exploratory subgroup analysis using the three statistically significant prognostic factors: the PFS index = summation of those three factors, each denoted as 0 or 1 [primary site nasopharynx (1) or not (0), PTV volume $<$ 40 cm³ (1) or not (0), and absence of ulceration (1) or not (0)]. The 2-year survival rates were: not available for Index 0 ($n = 14$; 9% at 7.6 months); 14% (95% CI, 0.01–28%) for Index 1 ($n = 32$); 43% (95% CI, 24–62%) for Index 2 ($n = 38$); and 64% (95% CI, 43–84%) for Index 3 ($n = 25$) ($P < 0.0001$, Fig. 1b). Cox's regression model revealed that the hazard ratio of the index group 3 was 2.07 (95% CI, 0.98–4.36,

$P = 0.05$), 4.308 for the index group 2 (95% CI, 2.03–9.12, $P = 0.0001$) for index group (1), and 17.4 (95% CI, 6.59–45.8, $P < 0.0001$) for control index group 0. This risk classification system separated the risk groups well (Fig. 1b).

Toxicity

A total of 22 patients (21%) presented with \geq Grade 3 toxicities, including 5 with fistulas, 2 with temporal lobe necrosis, 1 with bone necrosis/abscess, 5 with skin ulceration (with or without necrosis), 1 with visual disturbance, and 1 that required long-term percutaneous endoscopic gastrostomy (Table 4). There were 11 incidences of CBOS, resulting in nine deaths. A total of 2 CBOS patients were treated with interventional radiology procedures and manual compression. We examined clinical characteristics that may have predisposed patients to CBOS and identified ulceration as the only statistically significant predictor (Table 5). CBOS occurred in 6 patients with ulceration (6/25; 24%), whereas 5 patients experienced CBOS without ulceration (5/82; 6%; $P = 0.027$). The median duration between reirradiation and CBOS occurrence was 4.2 months (range: 0.9–27.5 months).

Table 2. Analysis of prognostic factors for overall survival rate after reirradiation

Variable	Strata	<i>n</i>	MST	2-year OS	<i>P</i> -value
Age, years	≤ 70	78	12.3	28%	0.76
	> 70	29	14.4	25%	
Gender	Male	78	14.8	33%	0.69
	Female	29	10.6	44%	
Primary site	Nasopharynx	41	42.3	61%	<0.0001*
	Others	66	10.2	17%	
	Oropharynx	21	11	69%	
	Hypopharynx	11	11.5	49%	
	Oral	14	7	13%	
	Nasal and sinus	20	10.1	20%	
Ulceration	Yes	25	6.6	8%	<0.0001*
	No	82	19.5	43%	
Previous surgery	Yes	47	14	27%	0.61
	No	60	17.7	41%	
PTV	≤ 40 cm ³	47	20.8	43%	0.001*
	> 40 cm ³	60	7.1	26%	
Prescribed dose (EQD2)	≤ 40 Gy	56	10.1	31%	0.02*
	> 40 Gy	51	19.4	41%	
Treatment interval	≤ 30 months	71	11.5	24%	0.02*
	> 30 months	36	28.2	58%	

MST = median survival time, PFS = progression-free survival, NA = not available, EQD2 = equivalent dose in 2-Gy fractions. *Asterisks indicate statistical significance. Nasopharynx vs others.

Table 3. Results of multivariate analysis according to overall survival after reirradiation

Variable	Strata	Hazard ratio	95% confidence interval	P-value*
Primary site	Nasopharynx vs other	2.42	1.37–4.28	0.002*
PTV	≤40 cm ³ vs >40 cm ³	1.96	1.19–3.21	0.007*
Prescribed dose (EQD2)	≤40 Gy vs >40 Gy	1.56	0.94–2.60	0.08
Treatment interval	≤30 months vs >30 months	1.56	0.86–2.70	0.14
Ulceration	yes vs no	2.7	1.53–4.76	0.0006*

EQD2 = biologically equivalent dose calculated into equivalent 2-Gy fractions $\alpha/\beta=10$. *Asterisks indicate statistical significance.

Table 4. Late toxicity

Grade 3 toxicity (no. of patients) ^v	Grade 4 toxicity (no. of patients)	Grade 5 toxicity (no. of patients)
PEG dependency (2)	Skin ulceration/ necrosis (1) ^a	CBOS (9)
Fistula (4)	CBOS (1)	
Temporal lobe necrosis (2)		
Bone necrosis/abscess (1)		
CBOS (1)		
Skin ulceration (2) ^b		
Visual disturbance (1)		

PEG = percutaneous endoscopic gastrostomy, CBOS = carotid blow-out syndrome.
^aOne patient showed simultaneously skin ulceration/necrosis requiring debridement and CBOS. ^bOne patient showed both skin ulceration and CBOS.

DISCUSSION

Long-term survival (>5 years) has become common for patients with head and neck cancer with the advent of improved treatment modalities and chemotherapy. However, a substantial number of patients develop in-field recurrence or adjacent primary cancers [1]. The management of recurrence in the head and neck remains challenging due to the high doses of radiation therapy required during initial curative treatment of the primary disease [2, 3]. CyberKnife is a novel modality that delivers precise doses with a shallow dose gradient. Several groups have investigated treatment with CyberKnife SBRT, including ours [6–9], and have demonstrated reduced acute toxicity due to short treatment periods and limited irradiation fields [6–9].

Late adverse events are most likely to limit the potential of this technique. For example, CBOS is one of the most devastating toxicities that can occur following reirradiation. Chloe *et al.* reported that 15 out of 33 treatment-related deaths (40%) were related to CBOS in 166 patients (15/166; overall rate = 9%) [12]. We also found 8.4% of CBOS among 381 head and neck carcinoma patients treated with 484 reirradiation sessions at seven Japanese CyberKnife institutions, and 69% of them were fatal [10]. In addition, the presence of ulceration associated with carotid invasion of >180° was an important risk

Table 5. Analysis of prognostic factors for carotid blow-out syndrome (CBOS)

Variable	Strata	n	CBOS (+)	CBOS (–)	P-value
Age, years	≤70	78	11	67	0.075
	>70	29	0	29	
Gender	Male	78	72	6	0.27
	Female	29	24	5	
Primary site	Nasopharynx	41	3	38	0.63
	Others	66	8	58	
Ulceration	Yes	25	7	18	0.0031*
	No	82	4	78	
Previous surgery	Yes	47	7	40	0.28
	No	60	4	56	
PTV	≤40 cm ³	47	7	40	0.28
	>40 cm ³	60	4	56	
Prescribed dose (EQD2)	≤40 Gy	56	7	49	0.63
	>40 Gy	51	4	47	
Treatment interval	≤30 months	71	5	66	0.22
	>30 months	36	6	30	

*Asterisk indicates statistical significance. EQD2 = equivalent dose in 2 Gy fractions.

factor for CBOS [11]. Therefore, we examined the predisposing factors for survival, including ulceration, in the current study.

Previously reported prognostic factors after reirradiation include nasopharyngeal primary site versus other sites [13, 14], radiotherapy

interval [6, 15], irradiated dose [14, 16], tumor volume [8, 17], presence of comorbidities, tumor burden [18], and resectability [14, 16, 19]. Ulceration is a well-known prognostic factor in patients who have received initially curative radiotherapy for head and neck cancer. Ulceration represents an invasive tumor characteristic and is regarded as a poor prognostic factor in the pretreatment of head and neck cancer patients [20]. Thus, it is plausible that infiltrative tumor characteristics influence prognosis, including toxicity, even following reirradiation. In addition, because CBOS was the only lethal toxicity found after reirradiation, it is quite natural that ulceration influenced OS through CBOS. Therefore, we believe ulceration as a tumor factor should be considered an important prognostic and risk factor, not only for CBOS [11] but also for OS. Hypofractionated SBRT, therefore, may not be a good candidate therapy for larger tumors with ulceration because their prognosis is poor, and informed consent including explanation of lethal CBOS (especially with carotid invasion of more than 180 degrees) incidence should be obtained for cases in which radiotherapy is considered [11].

There were several limitations to this study. First, this is a retrospective review including a number of disease sites; thus, selection- and physician-based bias may exist. Second, we were unable to analyze the details of previous chemotherapy and/or surgery because of the large heterogeneity in reporting practices between institutions. A prospective trial with a larger number of patients and longer follow-up should be performed to confirm our findings. In addition, several trials have investigated strategies to improve the outcome of reirradiation. For example, treatment on alternate days has been shown to reduce toxicity compared with daily treatment. Several authors have reported prospective trials using an alternate-days schedule with lower toxicity than that of our report [8, 9]. Furthermore, they used concurrently new therapeutic agents, such as cetuximab, to enhance efficacy. Although their data do not show a better OS than those reported in our study, we plan to change daily treatment to alternate-days treatment to reduce the incidence of CBOS in the future.

In conclusion, ulceration is an important prognostic factor, not only for adverse events but also for survival after reirradiation using CyberKnife.

SUPPLEMENTARY DATA

Supplementary data are available at [Journal of Radiation Research online](#).

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REFERENCES

- Mazeron R, Tao Y, Lusinchi A, et al. Current concepts of management in radiotherapy for head and neck squamous-cell cancer. *Oral Oncol* 2009;45:402–8.
- Vokes EE, Weichselbaum RR, Lippman SM, et al. Head and neck cancer. *N Eng J Med* 1993;328:184–94.
- Temam S, Pape E, Janot F, et al. Salvage surgery after failure of very accelerated radiotherapy in advanced head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2005;62:1078–83.
- Wong SJ, Machtay M, Li Y. Locally recurrent, previously irradiated head and neck cancer: concurrent reirradiation and chemotherapy, or chemotherapy alone? *J Clin Oncol* 2006;24:2653–8.
- Hoebbers F, Heemsbergen W, Moor S, et al. Reirradiation for head-and-neck cancer: delicate balance between effectiveness and toxicity. *Int J Radiat Oncol Biol Phys* 2011;81:e111–18.
- Kodani N, Yamazaki H, Tsubokura T, et al. Stereotactic body radiation therapy for head and neck tumor: disease control and morbidity outcomes. *J Radiat Res* 2011;52:24–31.
- Cengiz M, Ozyigit G, Yazici G, et al. Salvage reirradiation with stereotactic body radiotherapy for locally recurrent head-and-neck tumors. *Int J Radiat Oncol Biol Phys* 2011;81:104–9.
- Vargo JA, Ferris RL, Ohr J, et al. A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated recurrent squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2015;91:480–8.
- Lartigau EF, Tresch E, Thariat J, et al. Multi institutional phase II study of concomitant stereotactic reirradiation and cetuximab for recurrent head and neck cancer. *Radiother Oncol* 2013;109:281–5.
- Yamazaki H, Ogita M, Kodani N, et al. Frequency, outcome and prognostic factors of carotid blowout syndrome after hypofractionated re-irradiation of head and neck cancer using CyberKnife: a multi-institutional study. *Radiother Oncol* 2013;107:305–9.
- Yamazaki H, Ogita M, Kodani N, et al. Carotid blowout syndrome in Pharyngeal Cancer Patients treated by hypofractionated stereotactic re-irradiation using CyberKnife: a multi-institutional matched-cohort analysis. *Radiother Oncol* 2015;115:67–71.
- Choe KS, Haraf DJ, Solanki A, et al. Prior chemoradiotherapy adversely impacts outcomes of recurrent and second primary head and neck cancer treated with concurrent chemotherapy and reirradiation. *Cancer* 2011;117:4671–8.
- Lee N, Chan K, Bekelman JE, et al. Salvage reirradiation for recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys* 2007;68:731–40.
- Ohizumi Y, Tamai Y, Imamiya S, et al. Prognostic factors of reirradiation for recurrent head and neck cancer. *Am J Clin Oncol* 2002;25:408–13.
- Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multiinstitutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. *Head Neck* 2008;30:281–8.
- Salama JK, Vokes EE, Chmura SJ, et al. Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2006;64:382–91.
- Wu SX, Chua DT, Deng ML, et al. Outcome of fractionated stereotactic radiotherapy for 90 patients with locally persistent and recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2007;69:761–9.
- Tanvetyanon T, Padhya T, McCaffrey J, et al. Prognostic factors for survival after salvage reirradiation of head and neck cancer. *J Clin Oncol* 2009;27:1983–91.
- Unger KR, Lominska CE, Deeken JF, et al. Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2010;77:1411–19.
- Yamazaki H, Inoue T, Yoshida K, et al. Lymph node metastasis of early oral tongue cancer after interstitial radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;58:139–46.