Head and Neck

Reirradiation of recurrent head and neck cancer using high-dose-rate brachytherapy

Re-irradiazione mediante brachiterapia ad alte dosi nelle recidive dei tumori della testa e del collo

V. RUDZIANSKAS[1], A. INCIURA[1], E. JUOZAITYTE[1], M. RUDZIANSKIENE[1], R. KUBILIUS[2], S. VAITKUS[3], M. KASETA[3], D. ADLIENE[4]

[1] Lithuanian University of Health Sciences, Oncology Institute; [2] Lithuanian University of Health Sciences, Department of Maxillofacial Surgery; [3] Lithuanian University of Health Sciences, Department of Otorhinolaryngology; [4] Kaunas University of Technology, Physics Department, Kaunas, Lithuania

SUMMARY

The aim of the present study was to evaluate the results of hypofractionated accelerated CT-guided interstitial HDR-BRT using 2.5 Gy per fraction. From December 2008 to March 2010, 30 patients were treated for recurrence of previously-irradiated head and neck cancer. Thirteen patients underwent surgical resection followed by HDR-BRT to the tumour bed. Seventeen patients were treated with HDR-BRT only. All patients received 2.5 Gy twice per day for a total dosage of 30 Gy. The overall survival rate (OS) for the entire group at 1 and 2-years was 63% and 47%, while local control (LC) was 73% and 67%, and disease-free survival (DFS) was 60% and 53%, respectively. Patients treated with surgical resection and HDR-BRT showed an improvement in both 2-year LC (77% *vs*. 47%, p = 0.013) and 2-year OS (62% *vs*. 35%, p = 0.035) compared to patients treated with HDR-BRT only. Median OS for pre-treatment tumour volumes ≤ 36 cm^3 was 22 months and 9.2 months for those > 36 cm^3 (p = 0.038). Grade III and IV late complications occurred in 3% of patients. There were no grade V complications. The interstitial HDR brachytherapy regimen using 2.5 Gy twice daily fractions at a total dose of 30 Gy offers an effective treatment option for patients with recurrent previously-irradiated head and neck cancer with a low rate of late high grade toxicity. Surgical resection had a positive effect on survival and local control in management of patients with recurrent head and neck cancer.

KEY WORDS: Head and neck cancer • HDR brachytherapy • Reirradiation

RIASSUNTO

L'obbiettivo dello studio è stato valutare i risultati della brachiterapia interstiziale ipofrazionata TC guidata ad alte dosi (HDR-BRT) applicata con schema accelerato e frazioni di 2,5 Gy. Nel periodo di tempo compreso fra dicembre 2008 e marzo 2010 sono stati re-irradiati 30 pazienti affetti da recidiva di tumore della testa e del collo in esiti di pregressa radioterapia. Tredici di questi pazienti sono stati sottoposti ad una resezione chirurgica seguita da HDR-BRT sul letto tumorale. Diciassette pazienti sono stati trattati con HDR-BRT esclusiva. A tutti i pazienti è stata somministrata una dose di 2,5 Gy due volte al giorno fino al raggiungimento di 30 Gy di dose complessiva. La sopravvivenza globale considerando l'intero gruppo è stata del 63% al primo anno e del 47% al secondo anno di follow-up. Il controllo locale, invece, rispettivamente del 73% e del 67% dei casi; la sopravvivenza specifica per malattia infine è stata rispettivamente del 60% e del 53% dei casi. I pazienti trattati mediante resezione chirurgica più HDR-BRT presentavano rispetto ai pazienti trattati con HDR-BRT esclusiva un miglior controllo locale di malattia a due anni (77% vs. 47%, p = 0.013) ed una migliore sopravvivenza globale a due anni (62% vs. 35%, p = 0.035). La sopravvivenza mediana globale è stata di 22 mesi per tumori di dimensioni pre-trattamento ≤ 36 cm^3 e di 9,2 mesi per quelli > 36 cm3 (p = 0.038). Il 3% dei pazienti ha presentato complicanze tardive di III e IV grado, mentre nessuno ha mostrato complicanze di V grado. La scelta della brachiterapia interstiziale HDR applicata in frazioni da 2,5 Gy al giorno fino ad un totale di 30 Gy si è dimostrata essere un'efficace opzione terapeutica nei pazienti con tumore recidivante della testa e del collo in esiti di radioterapia, mostrando per altro un basso rischio di tossicità tardiva di alto grado. La resezione chirurgica ha avuto un effetto positivo nella gestione dei pazienti con recidiva di tumore della testa e del collo in termini di sopravvivenza e controllo locale di malattia.

PAROLE CHIAVE: *Tumori della testa e del collo • Brachiterapia ad alte dosi (HDR) • Re-irradiazione*

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Introduction

The majority of patients with head and neck carcinoma (HNC) have a locally advanced stage at diagnosis, and multimodality treatment is recommended for these patients, i.e., radiotherapy in combination with surgery, chemotherapy and/or biological therapy. Despite radical treatment, the incidence of recurrence may be as high as 30-50% in patients treated with curative intent [1 2]. The main treatment for recurrent disease is salvage surgery and re-irradiation [3-5]. In most cases, surgery is not feasible due to the high risk of complications and morbidity, and only 20% of patients are suitable for surgical salvage [6 7]. The possibilities for re-irradiation with an external beam are limited by normal tissue complications.

Brachytherapy can be used as an alternative treatment method for these patients. However, most reports present results using low dose-rate brachytherapy (LDR-BRT) [8-11]. During high-dose-rate brachytherapy (HDR-BRT), high doses of radiation can be delivered to the tumour volume directly, and rapid dose fall-off above planning treatment volume (PTV) allows for sparing of normal tissue. In most studies, the fraction doses of 3-4 Gy twice daily were used at a total dose of 18-48 Gy for treatment of patients with recurrent head and neck cancer [4 12-14]. To reduce late severe toxicity, we used a smaller fractionation, namely 2.5 Gy twice per day for a total dose of 30 Gy.

The aim of this study was to evaluate the results of hypofractionated accelerated CT-guided interstitial HDR-BRT using 2.5 Gy per fraction.

Materials and methods

Patients

Thirty patients were treated with hypofractionated interstitial HDR-BRT for locoregional relapse of head and neck carcinoma between December 2008 and March 2010. The study population included 21 males and 9 females with a mean age of 59 years (range, 41-79 years). Squamous cell carcinoma was confirmed in all patients. All patients had previous external beam radiotherapy (EBRT) or chemoradiation of the head and neck (median dose 66 Gy; range, 50-72 Gy). Twenty (70%) patients had undergone surgery as initial treatment, and 11 (37%) had surgery with neck dissection. For 9 (30%) patients, chemoradiation was performed in conjunction with cisplatin (100 mg/m^2, days 1, 22 and 43 of radiation therapy). Patient characteristics are shown in Table I.

The median time from the end of primary treatment to recurrence was 12 months (range, 3-19 months). Before re-irradiation, all patients were evaluated for eligibility and the following selection criteria was applied: 1) histologic evidence of disease relapse; 2) Karnofsky performance score (KPS) ≥ 80; 3) no bony invasion by the tumour; 4) no evidence of distant metastases. Thirteen (43%) patients

Table I. Patient characteristics.

Characteristic	n = 30	%
Gender		
Male	21	70
Female	9	30
Age (years)		
Median	59	
Range	41-79	
Primary tumour and lymph node stages		
T1-T2	15	50
T3-T4	15	50
N0	9	30
N1-N2	17	57
N3	4	13
Primary tumour site		
Oropharynx	5	17
Hypopharynx	2	7
Oral cavity	12	40
Larynx	1	3
Parotid	1	3
Nasal cavity/sinus	6	20
Lip	2	7
Unknown primary	1	3
Primary treatment		
EBRT only	4	13
Surgery and EBRT	17	57
EBRT and Cht	6	20
Surgery, EBRT and Cht	3	10
Radiation dose (Gy)		
Median	66	
Range	50-72	
Time to relapse (months)		
Median	12	
Range	3-43	

EBRT = external beam radiotherapy; Cht = chemotherapy.

Table II. Details of recurrent disease and implant characteristics.

Characteristic	n = 30	%
Treatment		
HDR-BRT alone	17	57
Surgery and HDR-BRT	13	43
Implant location		
Oral cavity	8	27
Nasal cavity/sinus	4	13
Parotid bed	1	3
Oropharynx	4	13
Neck	13	44
PTV Volume (cm^3)		
Median	36	
Range	8-107	
Re-irradiation dose (Gy)		
For all patients	30	

HDR-BRT = high dose rate brachytherapy; PTV = planned tumour volume.

underwent surgical resection followed by HDR-BRT, while the remaining patients were treated with HDR-BRT alone. The median implant volume was 36 cm^3 (range, 8-107 cm^3). Details of recurrent disease and implant characteristics are presented in Table II.

Brachytherapy

Surgical resection was performed for 13 of these patients. The area at risk was identified by a surgeon and radiation oncologist. A straight stainless-steel needle was introduced through the skin 10 mm away from the margin of intended target. The needle traversed the operative bed and then exited the skin on the opposite side of the operative bed. A plastic catheter was threaded through the needle and then the needle was removed, leaving the catheter in place. The number of catheters varied according to the dimension of the target. The plastic catheters were placed in the operative bed as near parallel as possible at 10 to 15 mm intervals with a security margin of 10 mm in all directions about the target. The catheters were held to the underlying musculature with absorbable sutures and attached at the skin exit points with plastic buttons and silk sutures. This implantation technique was used for the recurrence of the neck, nasal cavity/sinus and parotid bed.

For local relapse of the oral cavity and oropharynx loop, the implant technique was performed. During this procedure, steel needles were inserted on both side of the mandible through the neck in the region of the tumour volume. The plastic catheter was threaded through both intraoral ends of the needles. The steel needles were then removed leaving the catheter in place, which was fixed with plastic buttons. Spacing for these implants was between loops of 10 and 15 mm. The catheters were implanted as parallel as possible in order to encompass the tumour volume.

After the implant procedure, all patients underwent a computed tomography (CT) scan with a slice thickness of 2.5 mm for three dimensional (3D) treatment planning. Intravenous contrast was used when necessary to visualize the carotid vessels. The CT study was transferred to the Oncentra (Nucletron, The Netherlands) planning system, and PTV and organs at risk (OAR) (mandible, spinal cord, carotid vessel and larynx) were contoured and catheters were reconstructed. The treatment planning process followed the general rules of the Paris system, with manual optimization for each of the CT slices (Fig. 1).

Dose homogeneity within PTV and dose to OARs were documented using dose-volume histogram (DVH). Prescribed and reported doses were specified by D_{90} as determined by DVH. Dose heterogeneity was specified by V_{100} (the percentage of implant volume receiving 100% of the prescribed dose), V_{150} (the percentage of implant volume receiving 150% of the prescribed dose), V_{200} (the percentage of implant volume receiving 200% of the prescribed dose) [15]. In our series, the mean values were: D_{90} = 2.25 Gy (range, 1.9-2.5 Gy), equivalent to 90.2% of the reference dose of 2.5 Gy; V_{100} = 69.53% (range, 42-95%); V_{150} = 25.17% (range, 14-44%); V_{200} = 13.32% (range, 9-28%). The mean values of Homogeneity Index (HI) and Dose Non-Uniformity Ratio (DNR) were estimated to be 0.66 (range, 0.59-0.7) and 0.35 (range, 0.28-0.37) respectively. All patients were treated with a Nucletron Micro-Selectron HDR machine (Nucletron, The Netherlands) and received two daily fractions of 2.5 Gy for a total dose of 30 Gy with an interfraction interval of 6 hours.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (Statistical Package for Social Sciences 17.0 for Windows) statistical software. Survival results were calculated using the Kaplan-Meier method and log-rank test. The time origin was the date of the first HDR-BR procedure. The endpoint of overall survival (OS) was death from any cause. The endpoint of disease-free survival (DFS) was any type of recurrence (e.g. failure at the primary site or regional lymph nodes, distant metastasis). The endpoint of interest from local control (LC) was defined as tumour regrowth in the treated area with brachytherapy or in an adjacent region (e.g. failure at the primary site or regional lymph nodes).

Toxicities were documented according to the Radiation Therapy Oncology Group (RTOG) morbidity scoring criteria [16]. Toxicities from the date of the first brachytherapy implant to 90 days after the completion of the treatment were defined as acute. Toxicities were defined as late if they occurred more than 90 days after the last HDR-BRT fraction.

Follow-up

Overall follow-up ranged from 20 to 32 months (median 28 months) for survivors and 4-22 months (median 9 months) for fatalities. 19 patients reached the one-year follow up. 14 patients reached the two-year follow-up, and these patients were alive at the time of reporting in August 2011.

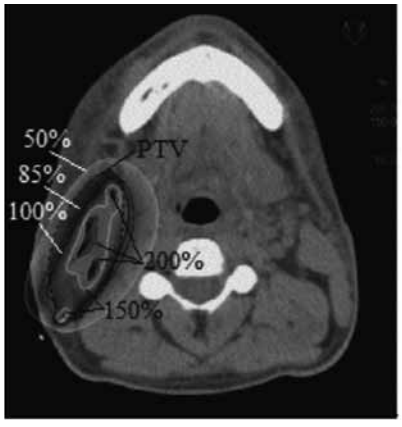

Fig. 1. Axial CT-image showing the PTV (dotted line) with values of isodoses.

Results

Local control

After a median follow-up of 16 months (range, 4-32 months), 14 (47%) patients had progression of neck disease. Of those, 4 patients had disease progression in the re-irradiated area, 8 patients had progression outside the implanted volume and 2 patients had distant metastases (one with pulmonary and another with cerebral metastases).

The LC and DFS rates for the entire group at 1 year and 2 years were 73% and 67%, 60% and 53%, respectively. The patients treated with surgical resection and HDR-BRT showed improvement in 2-year LC compared to those treated with HDR-BRT only (77% *vs*. 47%, p = 0.013).

Overall survival

The OS rate for the entire group was 63% at one year, and 47% at two years. The group treated with surgical resection and HDR-BRT had improved better two year OS compared with those treated with HDR-BRT alone (62% *vs*. 35%, p = 0.035) (Fig. 2).

Prognostic factors

Pre-treatment implant volume range was 8-107 cm^3 with a median value of 36 cm^3. Using this value, median overall survival for volumes ≤ 36 cm^3 was 22 months *vs.* 9.2 months for tumours > 36 cm^3 (p = 0.038), but there was no statistically significant correlation between pre-treatment volume and LC. Moreover, there was no statistically significant correlation between OS and the primary tumour site, primary T-stage or N-stage. This study failed to show a statistically significant correlation between LC and primary tumour site, primary T-stage or N-stage.

Toxicity

As expected, most patients developed mild-to-moderate acute mucositis and skin reactions. No carotid blowouts or massive haemorrhage during treatment or thereafter were seen. Two patients (7%) developed RTOG grade II acute toxicity and two (7%) grade II late toxicity (Table III). One of 30 patients (3%) developed RTOG grade III acute toxicity. This patient had delayed wound healing at the site of the steel needle insertion. A grade IV late complication was observed in one patient (3%). The patient with osteoradionecrosis of the mandible was treated with EBRT (total dose was 60 Gy) 10.6 months after brachytherapy was performed. The osteoradionecrosis developed over 3.5 months after the last fraction of brachytherapy and was treated by surgery. Revising the treatment plan, it was observed that one of five brachytherapy catheters was located near the mandible (< 5 mm), and the 110% isodose encompassed 5.7% volume of mandible (total volume 34.56 cm^3). We believe that this complication was due to brachytherapy, since before brachytherapy, a CT scan showed no lesion of the mandible. There was no grade V (fatal) toxicity.

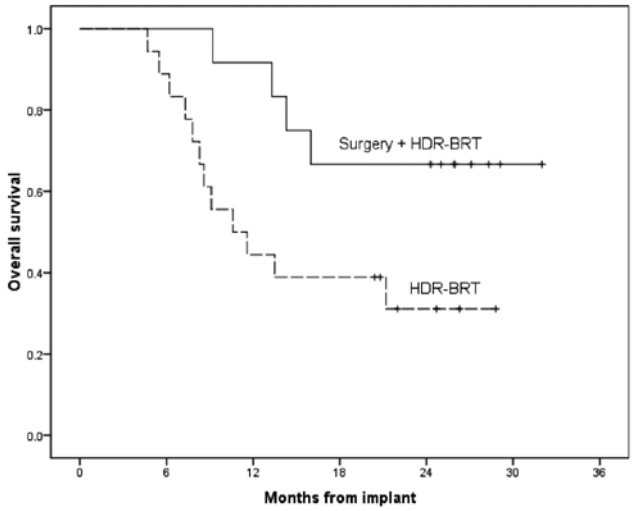

Fig. 2. Kaplan-Meier curves for overall survival based on HDR-BRT ± surgery.

Discussion

The standard treatment for recurrent head and neck tumours is salvage surgery, but in clinical practice there are some limitations. If recurrent tumours involve deep structures such as the scull base, nasopharynx, eustachian tube, mediastinal structures, prevertebral fascia or cervical vertebrae, then complete resection is precluded. The other restrictions to radical salvage surgery are suspected invasion of the carotid artery or the upper oesophagus. Patients who undergo an organ-sparing approach for treatment of locally advanced hypopharyngeal cancer cannot rely on a second chance with surgery for salvage should disease recur [17,18]. In the case of inoperable disease, chemotherapy can be offered with relatively low response rates of 50% to 60% and with a median survival of 5 to 6 months [19,20]. Re-irradiation with external beam therapy may be effective, but is limited by normal tissue complications caused by cumulative radiation doses. In the RTOG 96-10 trial, patients were treated with EBRT and concurrent chemotherapy (5-fluoruracil and hydroxyurea). The OS at one and two years was 41.7% and 16.2%, respectively, with 7% grade V toxicity and 23% grade IV acute toxicity. The late severe toxicity rate was not reported [21]. In the RTOG 96-11 phase II trial of hyperfractionated EBRT with cisplatin and paxlitaxel, the OS at one and two years were 50.2% and 25.9%, respectively. The incidence of grade V toxicity was 8% and 15%, respectively. Grade IV acute toxicity was reported. The incidence of osteonecrosis was 5% [22]. Using EBRT for re-irradiation, grade V toxicity was observed in both trials with a high grade IV toxicity rate. Using intensity-modulated radiotherapy (IMRT) for re-irradiation of recurrent head and neck disease, it is possible to reduce the toxicity of treatment. Some authors have reported OS at two years ranging from 35 to 58% and LC from 64 to 65%, with a toxicity rate of 13-

Table III. Toxicity.

Acute toxicities	n
Grade II	
Moderate fibrosis	2
Grade III	
Delayed wound healing	1
Late toxicities	**n**
Grade II	
Dysphagia	1
Persistent hoarseness	1
Grade IV	
Osteonecrosis	1

20% [23 24]. Similar results were reported using fractionated stereotactic radiotherapy, and the OS at two years ranged from 30% to 30.9% and LC from 41% to 52%, respectively, while the late severe toxicity rate ranged from 8.6% to 11% [25 26]. Recurrent head and neck cancer is more radioresistant compared to primary non-irradiated cancer. Therefore, a sufficient dose of irradiation must be delivered for the treatment of a recurrent tumour. Brachytherapy allows for delivery of a sufficient dose of radiation directly to the tumour while sparing the surrounding tissues.

Most authors report on the use of LDR-BRT, and there is only minimal data on the use of HDR-BRT for treatment of previously-irradiated head and neck cancers. Treatment results of LDR and HDR-BRT are summarized in Table IV.

Table IV. Published data on LDR and HDR-brachytherapy for recurrent cancer of the head and neck.

Study	Patients (N)	Salvage treatment	Toxicity Grade III-IV	Outcome/ comments
Kupferman et al. [27]	22	Surgery + ^{192}Ir-LDR-BRT median 60 Gy (range 20-60 Gy)	23%	1 y OS = 82% 2 y OS = 57% 5 y OS = 46% 2 y LC = 67%
Housset et al. [8]	23	^{192}Ir-LDR-BRT 65 Gy in two session separated by 1 month (35 Gy + 30 Gy)	36%, 4% Grade V toxicity	1 y OS = 26% 2 y OS = 13%
Bollet et al. [9]	84	a) ^{192}Ir-LDR-BRT mean 56.5 Gy (range 30-112 Gy) / (n = 72) b) ^{192}Ir-LDR-BRT + EBRT mean 38 Gy (range 23.6-50 Gy) / (n = 12)	35%, 7% Grade V toxicity	1 y OS = 33% 3 y OS = 13% 5 y OS = 1% 1 y LC = 49% 2 y LC = 31% 5 y LC = 0%
Cornes et al. [28]	39	Surgery + ^{192}Ir-LDR-BRT mean 49.5 Gy in 5 days	23%	2 y OS = 38% 1 y LC = 63%
Puthawala et al. [29]	220	^{192}Ir-LDR-BRT median 53 Gy (range 35-65 Gy)	27%	2 y OS = 43% 5 y OS = 20% 2 y LC = 69% 5 y LC = 51% 10 y LC = 41%
Hepel et al. [4]	30	^{192}Ir-HDR-BRT mean 34 Gy (range 18-48 Gy)	16%	1 y OS = 56% 2 y OS = 37% 1 y LC = 54% 2 y LC = 45%
Narayana et al. [12]	30	a) Surgery + ^{192}Ir-HDR-BRT 34 Gy / (n = 18) b) ^{192}Ir-HDR-BRT 40 Gy / (n = 9) c) EBRT 40-50 Gy + ^{192}Ir-HDR-BRT 20 Gy / (n = 3)	13% no Grade IV toxicities	2 y OS = 63% 2 y LC = 71%
Tselis et al. [13]	74	a) ^{192}Ir-HDR-BRT median 30 Gy (range 12-36 Gy) / (n = 69) b) ^{192}Ir-HDR-BRT + EBRT median 30.6 Gy (range 20-45 Gy) / (n = 5)	13%	1 y OS = 42% 2 y OS = 19% 3 y OS = 6% 1 y LC = 67% 2 y LC = 67% 3 y LC = 67%
Kolotas et al. [14]	49	^{192}Ir-HDR-BRT mean 31.5 Gy (range 30-36 Gy)	4% no Grade IV toxicities	1 y OS = 52% 2 y OS = 31% 3 y OS = 6%
Present study	30	a) Surgery + ^{192}Ir-HDR-BRT 30 Gy / (n = 13) b) ^{192}Ir-HDR-BRT 30 Gy / (n = 17)	3%	1 y OS = 63% 2 y OS = 47% 1 y LC = 73% 2 y LC = 67%

EBRT = external beam radiotherapy; 192Ir = iridium-192; OS = overall survival; LC = local control, LDR = low dose rate; HDR = high dose rate; BRT = brachytherapy.

The OS, LC and toxicity rates in our study are similar to LDR-BRT studies. A review of the literature with LDR-BRT suggests a two-year LC of 31-69% and OS of 13-57% in recurrent head and neck cancer [8 9 27-29]. In our study, OS at two years was 47% and LC was 67%. The severe complication rates in studies employing LDR-techniques ranged from 23% to 36%, including 7% grade V toxicity. In the present study, the late toxicity rate was lower compared with published LDR studies: grade III/IV toxicity was 3% and grade V toxicity was not observed.

The advantages of the HDR technique compared with LDR include better dose distribution homogeneity within the target volume, radiation safety and patient comfort. Only a few retrospective studies have been published regarding the re-irradiation of recurrent head and neck cancer using HDR brachytherapy [4 12-14]. Hepel et al. reported preliminary results in 30 patients with recurrent head and neck carcinoma. Patients were treated in twice daily fractions to a mean dose of 34 Gy (range, 18-48 Gy), with a dose per fraction of 3-4 Gy. Their study showed that OS at one and two years were 56 and 37%, respectively, with a LC of 54 and 45%, respectively [4]. Tselis et al. the HDR brachytherapy delivered a median salvage dose of 30.0 Gy (range, 12.0-36.0 Gy) in twice-daily fractions of 2.0-5.0 Gy for the majority of patients. The overall and disease-free survival rates at one, two and three years were 42%, 19% and 6%, and 42%, 37% and 19%, respectively [13]. Kolotas et al. reported on accelerated hyperfractionated interstitial HDR brachytherapy (2 x 3.0 Gy/day) delivered 30 Gy in 37 of 49 (75%) and 36 Gy in 24 of 49 implants (25%). After 19 months of follow-up, the local control rate was 69%. The overall survival rate was 52% at 1 year, 31% at 2 years and 6% at 3 years [14]. Narayama et al. treated 30 patients: 18 patients were operated following HDR-BRT using 3.4 Gy bid fractionation for a total dose of 34 Gy, nine patients were treated by HDR-BRT alone at 40 Gy (4 Gy bid) and for three patients EBRT (40-50 Gy) was combined with HDR-BRT (20 Gy, 4 Gy bid). The 2-year OS and LC for the entire group were 63% and 71%, respectively (12). In all of HDR BRT studies, the majority of patients were treated with daily fractions of 3 Gy for a total dose of 30 Gy or 4 Gy for a total dose of 40 Gy. To compare the results of different treatment schemes, we calculated the EQD2 (equivalent dose in 2 Gy fraction). For early effects, the α/β ratio was 10, and for late effects was 3 [30]. When calculating the EQD2 ($\alpha/\beta = 10$) of the HDR doses applied to these cases, the doses were 32.5 Gy or 46.7 Gy, respectively. In our study, the EQD2 ($\alpha/\beta = 10$) was 31.3 Gy, and overall survival, disease-free survival and local control results were similar to other studies, despite the fact that EQD2 ($\alpha/\beta = 10$) was lower.

Similar to other authors [13 14], we found that there was a statistically significant correlation between pre-treatment volume and OS. Tselis et al. study showed that OS for lesions < 65 cm^3 was 13 months, and for lesions ≥ 65 cm^3 was 6 months (p = 0.0001) (13). Kolotas et al. showed that median OS for lesions < 57 cm^3 was 19 months, and for lesions ≥ 57 cm^3 was 7 months (p = 0.002) [14]. In present study, median OS for volumes ≤ 36 cm^3 was 22 months, while it was 9.2 months for those > 36 cm^3 (p = 0.038). As in our study, neither of the above studies reported a statistically significant correlation between pre-treatment tumour volume and achieved LC rate. In all these studies, due to the small number of cases, heterogeneity of tumours and treatment methods, we did not observe a statistically significant correlation between OS and primary tumour site, primary T-stage and N-stage.

The results of our study show that patients treated with surgical resection and HDR-BRT had significant benefit considering two year OS (62% *vs*. 35%, p = 0.035) and LC (77% *vs*. 47%, p = 0.013) compared to patients treated with HDR-BRT only. The positive impact of surgical resection of a recurrent tumour to LC was noted by Narayama et al. (88% *vs*. 40%, p = 0.05), although it had had no impact on OS (70% and 43%, p = 0.66) [12]. In the other two studies (Schiefke et al., 2008 and Pellizzon et al., 2006), it was concluded that a combination of surgical resection and HDR-BRT improved the LC [18 31].

The grade III-IV toxicity rate after HDR brachytherapy was 4-16% [4 12-14]. The EQD2 ($\alpha/\beta = 3$) in HDR brachytherapy studies ranged from 36-56 Gy. To reduce the toxicity in our study, we used smaller doses per fraction, and the EQD2 ($\alpha/\beta = 3$) was 33 Gy. The lower EQD_2 might contribute to the lower late high grade toxicity compared with other studies. This study showed a relatively low grade III-IV toxicity rate (3%) and an absence of grade V toxicity.

In conclusion, our results suggest that interstitial HDR brachytherapy regimen using 2.5 Gy twice daily fractions to a total dose of 30 Gy can be offered as a treatment option for patients with recurrent previously-irradiated head and neck cancer. A combination of surgery and HDR-BRT has a positive effect on survival and local control. We recommend this approach for the management of patients with resectable recurrent head and neck cancer.

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Address for correspondence: Viktoras Rudzianskas, Lithuanian University of Health Sciences, Oncology Institute, Eiveniu 2, LT-50009, Kaunas, Lithuania. Tel. +37037326645. Fax +37037326625. E-mail: wictoras@hotmail.com