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Chapter 6

Re-irradiation for Recurrent Head and Neck Cancer

Viktoras Rudzianskas and
Rita Kupcinskaite-Noreikiene

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Abstract

After radical treatment of head and neck cancer about 20–50% of patients are diagnosed with the locoregional recurrence during first two years. The main treatment for recurrent disease is salvage surgery, but 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. Reirradiation is an effective treatment method with acceptable toxicity, but this treatment method is limited to normal tissue tolerance to a total dose. When chemotherapy is administered for recurrence, the response rate is up to 40%, so with the advancement of technical measures, after introduction of intensity-modulated radiotherapy, fractionated stereotactic body radiation therapy, high-dose-rate brachytherapy, proton beam reirradiation, a reirradiation is increasingly more often used for head and neck cancer relapse treatment. In this chapter, we will discuss about reirradiation with curative intent using new different radiation techniques (intensity-modulated radiotherapy (IMRT), stereotactic body radiation therapy (SBRT), high-dose-rate brachytherapy (HDR-BRT) and proton beam reirradiation (PBRT) for previously irradiated head and neck cancer and present recommendations for retreatment of head and neck cancer relapse using reirradiation alone or with systemic chemotherapy/biologic therapy.

Keywords: reirradiation, head and neck cancer, brachytherapy, proton beam therapy, stereotactic body radiation

1. Introduction

Despite the sophisticated methods of cancer diagnosis, more than 50% of cases are still diagnosed when the disease has reached III/IV stage. After radical treatment of head and neck cancer, about 20–50% of patients are diagnosed with the locoregional recurrence during first two years [1–3]. The main treatment for recurrent disease is salvage surgery, but in most cases, surgery is not feasible due to the high risk of complications and morbidity, and only 15–30%

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of patients are suitable for surgical salvage [4–8], and 5-year overall survival is 16–36% [9–14]. When chemotherapy is administered for recurrence, the response rate is up to 35–40%, and median overall survival is about 10% [15–17]. The results of retrospective studies presented in literature, using reirradiation by three-dimensional radiotherapy (3D-RT) for head and neck cancer recurrence, according to a 2-year overall survival and toxicity, are poor: overall survival reached 15.2–40%, the rate of severe late toxicities (grade 3 and 4) reached 1.4–47%, the rate of degree 5 (lethal) complications reached 7.6% [18–21]. However, with the advancement of technical measures, after introduction of intensity-modulated radiotherapy (IMRT), fractionated stereotactic body radiation therapy (F-SBRT), high-dose-rate brachytherapy (HDR-BRT), proton beam reirradiation (PBRT), a reirradiation is increasingly more often used for head and neck cancer relapse treatment [6, 18, 22–24].

In this chapter, we will discuss about reirradiation with curative intent using new different radiation techniques (IMRT, SBRT, HDR-BRT and PBRT) for previously irradiated head and neck cancer and present recommendations for retreatment of head and neck cancer relapse using reirradiation alone or with systemic chemotherapy/biologic therapy.

2. Reirradiation techniques and outcomes

2.1. Intensity-modulated radiotherapy and stereotactic body radiotherapy reirradiation

When comparing IMRT and F-SBRT against 3D-RT technique, it is possible to apply a larger radiation total dose during IMRT and F-SBRT, better protect adjacent tissues, while also achieving a better dose homogeneity. Lee et al. published results of 105 patients treated for head and neck cancer relapse using external beam radiation therapy [25]. Study included 74 (70%) patients treated with IMRT, 16 (15%) patients received conformal 3D radiation therapy and 15 (15%) patients received 2D radiation therapy. Prior to reirradiation, surgical treatment was performed on 36 (34%) patients, chemotherapy (mostly platinum-based) was administered to 75 (71%) patients, including 45 (43%) cases combined with radiation therapy. The median reirradiation dose was 59.4 Gy (range 30–70 Gy), median cumulative dose was 121.4 Gy (range 88–137 Gy). The 1-year and 2-year overall survival was 56% and 37%, respectively; locoregional control was 48% and 42%, respectively. The frequencies of early and late grade 3 and 4 toxicities were 23% and 15% (early and late, respectively). Sulman et al. conducted a retrospective analysis of 74 patients who were treated for head and neck cancer relapse and secondary cancer by applying IMRT to the previously irradiated area [24]. Before the reirradiation, 20 (27%) patients underwent surgery, 36 (48.6%) patients received chemotherapy: 23 patients received concurrent chemotherapy, four (11.1%) patients received induction chemotherapy, one (2.8%) patient received adjuvant chemotherapy, seven (19.4%) patients received induction and concurrent chemotherapy and one patient received concurrent and adjuvant chemotherapy. Platinum-based chemotherapy was administered to nine (25%) patients, 23 (64%) patients received a combined platinum- and taxane-based chemotherapy, three (8.3%) patients received platinum- and 5-fluorouracil-based treatment and one patient was administered a medication based on platinum with taxanes and lonafarnib (farnesyltransferase inhibitor). Median survival was 27.6 months; 2-year overall survival and

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locoregional control were 58% and 64%, respectively. Severe late toxicity (grade 3 and 4) was observed in 15 (20%) patients; one patient died (grade 5 toxic reaction). Duprez et al. published medical results based on 84 patients treated for recurrent or secondary head and neck cancer using IMRT [26]. Concurrent platinum-based chemotherapy was administered to 17 (20%) patients, 19 patients underwent surgical treatment and IMRT. Median dose delivered by IMRT was 69 Gy, median cumulative dose was 130 Gy (range 71–138 Gy). Median survival was 13.4 months; 1-year, 2-year and 5-year overall survival was 54%, 35%, and 20%, respectively; progression-free survival was 58%, 42%, and 29%, respectively. Severe early toxicity occurred in 26 (31%) patients, late toxicity occurred in 52 (62%) patients (grade 3 and 4 in 11 (13.1%) patients). Late grade 5 reactions occurred in two (2.4%) patients. It was determined during this study that T4 ($p = 0.013$), >2 years time interval between primary radiation therapy and reirradiation ($p = 0.011$), and hypopharyngeal cancer ($p = 0.013$) are statistically significant unfavorable factors impacting the overall survival, while the concurrent chemotherapy ($p = 0.0009$) is related to higher frequency of severe complications (grade 3 and 4). Chen et al. completed a retrospective study which included 21 patients [27]. All patients were diagnosed with recurrent head and neck cancer or secondary tumor, and IMRT was used in combination with image-guided radiation therapy (IGRT). The 1-year and 2-year overall survival was 65% and 40%, respectively. The authors identified severe acute toxicity frequencies: skin desquamation in 12 (57%) patients, dysphagia in 9 (42%) patients and mucositis in 5 (23%) patients. Late reactions: 2 patients were diagnosed with trismus, 1 patient was diagnosed with brachial plexopathy and gastrostomy was performed on 12 (57%) patients to manage swallowing disorder following the radiation therapy. Similar results were published for application of fractional stereotactic body radiation therapy (F-SBRT). Roh et al. treated 36 patients (44 areas) diagnosed with head and neck cancer relapse [28]. Median total dose was 30 Gy (range 18–40 Gy), delivered in 3–5 fractions over 3–5 days prescribed to the 65–85% isodose line. The 1-year and 2-year progression-free survival was 61% and 52.2%, respectively, while 1-year overall survival was 52.1%, 2-year survival was 30.9%. Early grade 3 reactions were diagnosed in 13 patients; late complications (grade 3 and 4) were diagnosed in 3 (8.6%) patients. Cengiz et al. used F-SBRT to treat 46 patients diagnosed with unresectable recurrent head and neck cancer [22]. Median total dose was 30 Gy (range 18–35 Gy), delivered mostly in five fractions (range 1–5 fractions). Overall 1-year survival and progression-free survival was 47% and 41%, respectively. Frequency of early toxicity was 4.4%: one patient was diagnosed with grade 3 dermatitis and grade 1–3 mucositis according to RTOG criteria; grade 5 complication frequency was 4.4%. Late reactions were diagnosed in six (13.3%) patients: two patients were diagnosed with soft tissue necrosis, two patients had osteonecrosis of the mandible and two patients were also diagnosed with grade 2 dysphagia. Five (11%) patients died due to bleeding from the carotid artery. Siddiqui et al. used stereotactic radiation therapy to treat 44 patients (55 areas), including 21 patients (29 cases) diagnosed with head and neck cancer relapse in primary tumor location or adjacent location [23]. Patients who were diagnosed with the relapse in regional neck lymph nodes where not included in this group. Delivered total dose was 36 Gy in 6 fractions or 48 Gy in 8 fractions, 2–3 fractions/week or 16–18 Gy single fraction. In this group of patients, 1-year and 2-year overall survival was 38.1% and 14.3%, respectively, local control was 60.6% and 40.4%, respectively. Early grade 3 toxicity was diagnosed in one patient; grade 4 complications were diagnosed in three patients.

In conclusion, it can be stated that the results of external beam reirradiation therapy used to treat head and neck cancer relapse, according to the treatment techniques, are: using IMRT, 2-year overall survival was 35–58%, locoregional control was 42–64%, 2-year progression-free survival reaches 42%, while the frequency of grade 3 and 4 toxicity was 13.1–20%, frequency of grade 5 radiotherapy reactions up to 2.8% [16, 25, 26, 28]. Results from F-SBRT studies: 2-year overall survival was 14.3–40%, local control 40.4%, progression-free survival was 52.2%, frequency of late severe complications was 8.6–14%, frequency of grade 5 complications was 2.8–14% [16, 22, 23, 28] (**Table 1**). During most of these studies, prognostic factors have been determined which influence the overall survival, locoregional control and progression-free survival; these factors were: longer time interval between initial radiation therapy and reirradiation; chemotherapy or biological therapy, administered in combination

Author	N	Treatment	Late toxicity grade 3–4	Results
Lee et al. [25]	105	(a) IMRT/(n = 74) (b) 3D-RT/(n = 16) (c) 2D-RT/(n = 15) 75 pts. received platinum-based CHT Median dose 59.4 Gy (30–70 Gy)	15%	1 y OS—56% 2 y OS—37% 1 y LRC—48% 2 y LRC—42%
Sulman et al. [24]	74	(a) Surgery + IMRT/(n = 20) (b) IMRT + CHT/(n = 36) (c) IMRT/(n = 48) Median dose 63 Gy (48.8–70 Gy)	20% Grade 5—2.8%	2 y OS—58% 2 y LRC—64%
Duprez et al. [26]	84	(a) OP + IMRT/(n = 19) (b) IMRT + CHT/(n = 17) (c) IMRT/(n = 48) Median dose 69 Gy	13.1% grade 5—2.4%	1 y OS—54% 2 y OS—35% 5 y OS—20% 1 y DFS—58% 2 y DFS—42% 5 y DFS—29%
Chen et al. [27]	21	IMRT, median dose 66 Gy (60–70 Gy)	Dysphagia—57%, trismus—9.5%, brachial plexopathy—4.8%	1 y OS—65% 2 y OS—40%
Roh et al. [28]	36	F-SBRT, median dose 30 Gy (18–40 Gy)	8.6% grade 5—2.8%	1 y OS—52.1% 2 y OS—30.9% 1 y LRC—61% 2 y LRC—52.2%
Cengiz et al. [22]	46	F-SBRT, median dose 30 Gy (18–35 Gy)	13.3% grade 5—11%	1 y OS—47% 1 y DFS—41%
Siddiqui et al. [23]	21*	F-SBRT/(n = 10): (a) 36 Gy/6 fx (b) 48 Gy/8 fx S-SBRT/(n = 11): Single-fraction 13–18 Gy	Grade 4—14%	1 y OS—38.1% 2 y OS—14.3% 1 y LC—60.6% 2 y LC—40.4%

Notes: 3D-RT, three-dimensional conformal radiotherapy; 2D-RT, two-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy; CHT, chemotherapy; F-SBRT, fractionated stereotactic body radiation therapy; S-SBRT, radiosurgery; OS, overall survival; LRC, locoregional control; DFS, disease free survival; LC, local control.

* 44 patients participated in study, but results are presented only for 21 patient treated for disease relapse.

Table 1. Summary of published data on IMRT and SBRT for recurrence from head and neck cancer.

with reirradiation therapy; total dose of reirradiation therapy ≥50 Gy and surgical treatment prior to reirradiation therapy. Frequency of severe toxicity (grade 3 and higher) statistically significantly depended on the following factors: chemotherapy, administered in combination with reirradiation therapy; total dose of reirradiation therapy >60 Gy.

Results of the discussed studies prove that it is possible to achieve good locoregional control with acceptable toxic reactions through application of external beam reirradiation therapy. Using IMRT method, the number of late radiation reactions was lower compared with 3D-RT or F-SBRT.

Recommendations for IMRT (**Figure 1**):

1. To use repeated IMRT to treat patients with good functional status (Karnofsky Performance Score ≥ 60) in combination with chemotherapy or biological therapy after surgery, when there are positive resection margins, extracapsular nodal spread, perineural or lymphovascular infiltration.
2. Minimal time interval between initial radiation therapy and reirradiation 6–12 months.
3. Reirradiation volume: PTV = GTV + 5 mm, total dose ≥50–60 Gy, using conventional fractionation (1.8–2 Gy/fx).

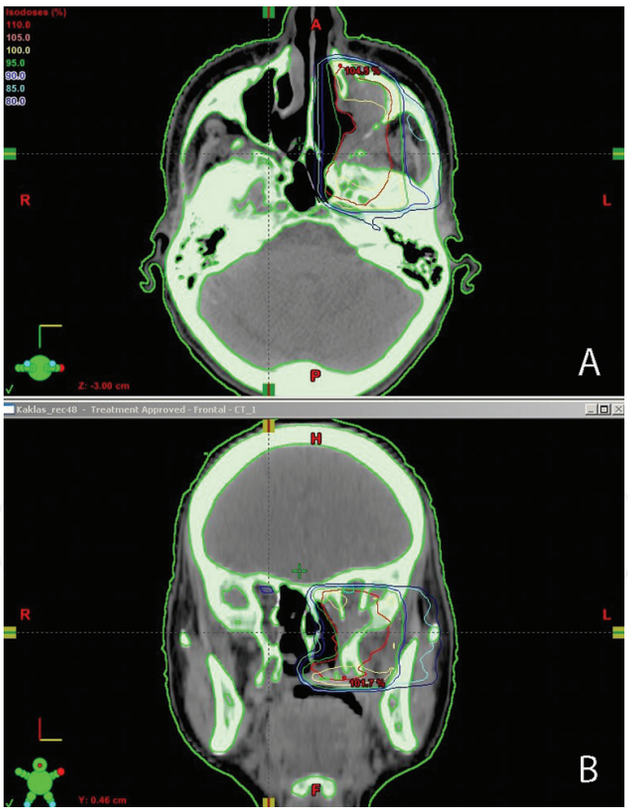


Figure 1. Representative isodose plan for patient undergoing reirradiation: (A) axial and (B) coronal CT slice. The patient had recurrent grade 3 adenoid cystic carcinomas of hard palate previously treated to 60 Gy with concurrent cisplatin. A local recurrence developed after 15 months, and the patient underwent reirradiation with IMRT to 48 Gy. The clinical and planning target volumes are showed in red, the total cumulative dose to brainstem was 51.54 Gy, spinal cord—42.1 Gy, chiasma—50.4 Gy, n. opticus left—51.2 Gy. No late toxicity was observed after 1 year.

Recommendations for F-SBRT (**Figure 2**):

1. To use repeated F-SBRT to treat patients with good functional status (Karnofsky Performance Score ≥ 60) in combination with chemotherapy or biological therapy after surgery, when there are positive resection margins, extracapsular nodal spread, perineural or lymphovascular infiltration.
2. F-SBRT is not recommended to treat laryngeal and hypopharyngeal site of recurrence due to higher frequency of late reactions.
3. Recommended total dose 35–42 Gy in 7 fractions prescribed to the 80–85% isodose line, over 2.5 weeks (total dose must not exceed 44 Gy).

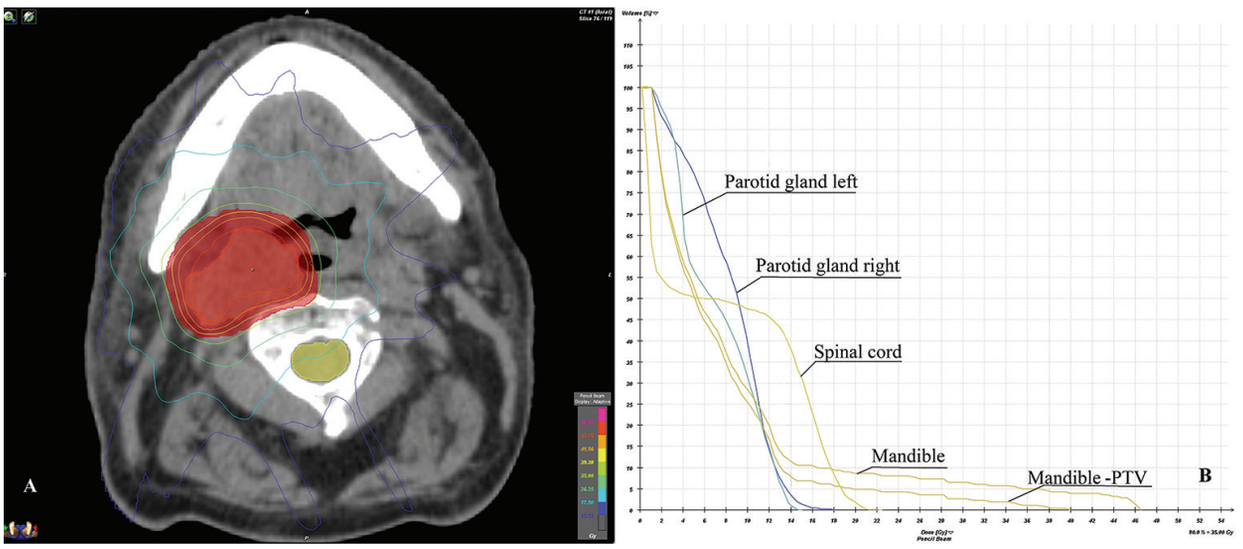


Figure 2. Dosimetric plan (A) used for reirradiation of a patient with recurrent oropharyngeal squamous cell carcinoma; dose-volume histogram is showed in apex (B). The patient underwent radical chemoradiotherapy as primary treatment (total dose 68 Gy/34 fx), after local recurrence developed approximately 21 months later, and the patient underwent reirradiation with F-SBRT—35 Gy/7 fx prescribed to the 80% isodose. The total cumulative dose to spinal cord was 57.8 Gy, mandible—93 Gy, larynx—72.4 Gy, parotid gland left—36 Gy, parotid gland right—72.4 Gy. No late toxicity was observed after 1.6 year.

2.2. High-dose-rate brachytherapy reirradiation

When using brachytherapy, it is possible to directly irradiate the tumor and deliver sufficient dose while also reducing the frequency of severe complications, such as trismus or severe xerostomia [29, 30]. In published studies, which involved patients with the diagnosis of head and neck cancer relapse and who were treated using HDR-BRT, different treatment regimens have been selected.

Hepel et al. published results of study involving 30 patients diagnosed with head and neck cancer relapse and treated using 192I-HDR-BRT [31]. All patients were treated using external beam radiation therapy, delivering mean dose of 59 Gy (range 23–75 Gy), with minimal 1-year follow-up. Adjuvant chemotherapy was administered to 43% patients, 36% were treated using hyperthermia therapy. Using HDR-BRT, two daily fractions have been prescribed with

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minimum 6-hour separation interval. In patients with implant volume adjoined to mucosa 3 Gy/fraction was delivered, and 4 Gy/fraction in other patients. Average administered total dose was 34 Gy (range 18–48 Gy), average implant volume 85 cm^3 (range 34–265 cm^3). Dose distribution was evaluated according to dose-volumes histogram (DVH), also ensuring that implant volume irradiated by 200% of the prescribed dose (V200) would not exceed 10% PTV. The 1-year and 2-year overall survival was 56% and 37%, respectively, local control was 69% and 67%, respectively, progression-free survival was 54% and 45%, respectively. Medium grade mucositis was diagnosed in most patients; late reactions (grade 3 and 4) were diagnosed in five (16%) patients: two were diagnosed with soft tissue necrosis, one had esophagocutaneous fistula, one had lower jaw bone necrosis and one patient was diagnosed with tongue atrophy and fibrosis along with speech disorder. No grade 5 complications occurred. Tselis et al. used the accelerated hypofractionated 192Ir-HDR-BRT to treat 74 diagnosed with isolated head and neck cancer relapse in neck [7]. Patients had previously received radiation therapy or chemoradiation therapy; administered median total dose was 60 Gy (range 22–72 Gy). Due to primary tumor, surgery was performed on 43 (58%) patients; lymphadenectomy was performed at the same time on 33 of these patients (45%). Median time interval after primary treatment until isolated relapse was 12 months (range 3–207 months). Median target volume was 64.7 cm^3 (range 6.4–622 cm^3). Prior to HDR-BRT, 9 (12%) patients have been treated using external beam radiation therapy, administered median dose 40 Gy (range 20–70 Gy); 48 (65%) patients received chemotherapy; five (8%) received surgical treatment. Median time interval between external beam reirradiation therapy, last palliative chemotherapy course, or surgery and the beginning of HDR-BRT was 221 days (range 68–476 days), 53 days (range 22–819 days) and 149 days (range 94–251 days), respectively. A total of 12 (16%) patients were not additionally treated following primary treatment until procedures of HDR-BRT. During HDR-BRT, median Karnofsky Performance Score was 80 (range 60–100). When performing HDR-BRT, 71 (96%) patients were prescribed two daily fractions with minimum 6-hour separation interval, and median delivered single fraction dose was 3 Gy (range 2–5 Gy). For remaining three (4%) patients, the median delivered single fraction dose was 6 Gy (range 6–10 Gy) delivered in one daily fraction. All patients were administered a median total dose of 30 Gy (range 10–36 Gy). A total of 69 (93%) patients were treated using stand-alone HDR-BRT; five (7%) patients received this treatment in combination with external beam radiation therapy; median prescribed dose was 30.6 Gy (range 20–45 Gy). Dose distribution was evaluated according to DVH with consideration of D90, and dose heterogeneity was assessed according to V100, V150 and V200. In 60 (81%) patients who were prescribed with single fraction dose of 3 Gy, evaluated dosimetric parameters were as follows: D90 = 2.9 Gy (range 2.1–3.7 Gy) = 96.7% of the administered dose. Resulting dosimetric parameters for all the patients: median D90—97.7% (range 70–123.3%); V100 = 88.8% (range 68.8–96.9%); V150 = 58% (range 42–76%) and V200 = 38% (range 21–58%). Radiotherapy toxicity was evaluated according to RTOG/EORTC criteria. Median overall survival was 42 weeks; 1-year, 2-year and 3-year overall survival reached 42%, 19% and 6%, respectively. The 1-year local control was 67%, 2-year—67% and 3-year—67%; 1-year, 2-year and 3-year progression-free survival was 42%, 37% and 19%, respectively. After determining that the median target volume was ~65 cm^3, patients were divided into two groups, and it was found that in patients with target volume <65 cm^3 survival reached 13 months compared to 6 months in patients with target volume ≥65 cm^3

($p = 0.0001$). In patients who were prescribed with a treatment dose of <32.5 Gy based on calculated EQD2, median survival was 9 months, while in patient group with accordingly calculated EQD2 ≥ 32.5 Gy median survival was 13 months ($p = 0.098$). In the scope of this study, no statistically significant difference has been found between patient survival and factors such as primary tumor location, histological type of tumor, T and N stages of the primary tumor. Also, no statistical significant difference has been determined between local control and primary tumor location, histological type of tumor, T and N stages of the primary tumor, tumor relapse volume, KPS or prescribed dose. Acute toxicity (grade 3 and 4) was diagnosed in 5% of patients; frequency of late complications (grade 3 and 4) reached 8%, including three diagnosed with fistula. No grade 5 complications were diagnosed. Narayana et al. used HDR-BRT to treat 30 patients diagnosed with recurrent head and neck cancer [32]. About 77% of all patients had been diagnosed with local or regional relapse in previously irradiated location. Prior to HDR-BRT, 18 patients received surgical treatment, and they were prescribed with a total dose of 34 Gy administered in two 3.4 Gy daily fractions. A total of nine patients were treated using stand-alone HDR-BRT; a total dose prescribed was 40 Gy in two 4 Gy daily fractions. Remaining three patients received external beam radiation therapy 40–50 Gy and HDR-BRT 20 Gy, delivering two 4 Gy daily fractions. Toxicity was evaluated according to RTOG and NCI-CTC Version 3 toxicity criteria. The 2-year overall survival and local control were 63% and 71%, respectively. In group of patients who received surgical treatment and HDR-BRT, 2-year local control was better compared to remaining patients (88% vs. 40%, $p = 0.05$), although no statistically significant difference has been found when comparing the overall survival in these groups (70% vs. 43%, $p = 0.66$). Early complications (grade 3 and 4) were diagnosed in four patients; late grade 2 toxicity was diagnosed in six (20%) patients, late grade 3 toxicity was diagnosed in four (13%) patients: soft tissue fibrosis in two cases, one patient was diagnosed with trismus and one patient was diagnosed with a strong constant pain requiring nerve blockade to suppress it. No toxic reactions grade 4 and 5 occurred. Pellizzon et al. published results from a retrospective study which involved 21 patients diagnosed with head and neck cancer relapse in neck lymph nodes [33]. A total of 15 patients (71.4%) previously had been treated using external beam radiation therapy, with median total administered dose of 52 Gy (range 30–66 Gy). Median time between initial and repeated treatments was 32 months (range 14–86 months). All patients received surgical treatment; median time between surgery and HDR-BRT was 5 days (range 4–12 days). 192Ir-HDR-BRT treatment planning and optimization has been carried out in accordance with the Paris System principles, ensuring that the "hot spots" in the quarter of PTV would not exceed 135% of prescribed dose, and the skin-affecting dose would not exceed 60% of prescribed dose. Median prescribed total dose was 35 Gy (range 12–48 Gy), number of fractions 3–16 (median—8 fractions). After HDR-BRT, patients underwent external beam radiation therapy; median time between these treatment stages was seven days (range 1–37 days). Median prescribed total dose was 45 Gy (range 30–66 Gy), and in patients who already had been treated using external beam radiation therapy median dose was 30 Gy (range 25–50 Gy). The 5-year and 8-year overall survival was 50% and 42.9%, respectively, disease free survival was 42.5% and 28.6%, respectively. During this study, only a single factor has been determined which influences overall survival and progression-free survival in statistically meaningful way ($p = 0.0002$ and

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p = 0.0007, respectively), and this prognostic factor is the condition of resection margin (positive vs. negative resection margin). About four (19.4%) patients were diagnosed with early radiation reactions, and four patients had severe late complications: three were diagnosed with local non-healing wounds, one patient had wide-neck tissue fibrosis. There were no cases of soft-tissue necrosis. Schiefke et al. treated 18 patients diagnosed with locally advanced head and neck cancer; treatment was carried out by performing tumor resection and delivering 192Ir-HDR-BRT [34]. A total of 5 patients were treated for primary head and neck cancer; 13 patients were treated for relapse. Out of 13, 10 patients who were diagnosed with cancer recurrence had radical tumor resection during initial treatment, eight of them had lymphadenectomy performed simultaneously; following surgery, external beam radiation therapy was administered with a total prescribed dose 59.4–69.9 Gy; one patient received adjuvant chemotherapy. All the patients included in this study received surgery by performing partial tumor resection and implantation of brachytherapy catheters, ensuring that the post-operative bed including 5 mm margin is covered by 100% isodose. Median time between surgery and HDR-BRT was 6 days (range 4–41 days), median total dose was 30 Gy (range 15–44.8 Gy), with median prescribed single fraction dose of 3 Gy (1.5–3.5 Gy); two daily fractions were prescribed with minimal interval of 8 hours. Median PTV volume was 103.1 cm^3 (range 25.4–220 cm^3). A total of eight patients additionally received external beam radiation therapy, total dose 6–49.6 Gy (median 45 Gy); 7 patients received chemotherapy. In patients treated for relapse, median survival was 22.8 months (range 2.4–43.8 months) and 2-year overall survival and progression-free survival was 59.8 and 64.8%, respectively. Median progression-free survival was 12.8 months (range 4–27 months). Severe late toxicity was diagnosed in four (22.2%) patients: one patient experienced bleeding from the carotid artery, one patient experienced abnormal healing of operating wounds and was diagnosed with fistula, two patients were diagnosed with osteonecrosis.

In published studies involving application of HDR-BRT to treat head and neck cancer relapse, 3 Gy fractions to total dose of 30 Gy, or 4 Gy fractions to total dose of 40 Gy have been delivered. Using these treatment regimens, 2-year overall survival was 19–63%, local control was 67–71%, progression-free survival was 37–64.8%, and the frequency of late grade 3 and 4 toxicity was 8–22.2%. No grade 5 reactions were diagnosed (**Table 2**).

Application of HDR-BRT is limited by technical possibilities to implant brachytherapy catheters, and therefore this method of therapy is suitable to treat lip, oral cavity, oropharyngeal cancers, and also is suitable for inoperable recurrent cervical lymphadenopathy.

Recommendations for HDR-BRT (**Figure 3**):

1. High-dose-rate brachytherapy is effective and safe method of treatment, which can be applied to treat local head and neck cancer relapse diagnosed in previously irradiated area, delivering total dose of 30–40 Gy in 3–4 Gy/fraction, in two daily fractions separated by minimum 6-hour interval.

2. High-dose-rate brachytherapy is recommended to treat head and neck cancer relapse if the relapse volume does not exceed 30–40 cm^3.

3. In order to avoid severe late radiotherapy complications and to ensure local control, it is recommended that: PTV volume is ≥5 mm away from bone structures; PTV volume irradiated by 200% of prescribed dose (V200) does not exceed 10% of total PTV; skin-affecting dose does not exceed 60% of prescribed dose; homogeneity index (HI) is no less than 0.6–0.7; dose non-uniformity ratio (DNR) is not higher than 0.25–0.35.

Author	N	Treatment	Late toxicity grade 3-4	Results
Hepel et al. [31]	22	192Ir-HDR-BRT median dose 34 Gy (18–48 Gy)/3–4 Gy/fx	16%	1 y OS—56% 2 y OS—37% 1 y DFS—54% 2 y DFS—45%
Narayana et al. [32]	39	(a) Surgery + 192Ir-HDR-BRT 34 Gy/(n = 18) (b) 192Ir-HDR-BRT 40 Gy/(n = 9) (c) RT 40–50 Gy + 192Ir-HDR-BRT 20 Gy/(n = 3)	13% No grade 4 toxicity	2 y OS—63% 2 y LC—71%
Tselis et al. [7]	100	(a) 192Ir-HDR-BRT, median dose 30 Gy (30–36 Gy)/(n = 69) (b) 192Ir-HDR-BRT+RT, median dose 30.6 Gy (20–45 Gy)/(n = 5)	8%	1 y OS—42% 2 y OS—19% 3 y OS—65% 1 y LC—67% 2 y LC—67% 3 y LC—67% 1 y DFS—42% 2 y DFS—37% 3 y DFS—19%
Pellizzon et al. [33]	84	(a) Surgery + 192Ir-HDR-BRT, median dose 35 Gy (12–48 Gy)/3–4 Gy/fx + RT, median dose 45 Gy (30–60 Gy)/(n = 6) (b) Surgery + 192Ir-HDR-BRT median dose 35 Gy (12–48 Gy)/3–4 Gy/fx + RT, median dose 30 Gy (25–50 Gy)/(n = 15)	19.4%	5 y OS—50% 8 y OS—42.9% 5 y DFS—42.5% 8 y DFS—28.6%
Schiefke et al. [34]	23	(a) Surgery+192Ir-HDR-BRT, median dose 30 Gy (15–44.8 Gy)/(n = 10) (b) Surgery+192Ir-HDR-BRT, median dose 30 Gy (15–44.8 Gy)+RT, median dose 45 Gy (6–49.6 Gy)/(n = 8)	22.2%	2 y OS—59.8% 2 y DFS—64.8%

Notes: 192Ir, iridium 192; HDR-BRT, high dose rate brachytherapy; RT, external beam radiotherapy; OS, overall survival; DFS, disease free survival; LC, local control.

Table 2. Summary of published data on interstitial high-dose-rate brachytherapy for head and neck cancer relapses.

2.3. Reirradiation with proton beam therapy

External beam radiation therapy extends survival in patients diagnosed with head and neck cancer; however, occurring xerostomia, dysphagia, impaired ability to sense taste, post-radiation caries worsens the quality of life [35]. It is likely that delivering repeated external beam radiation therapy in patients diagnosed with head and neck cancer relapse would lead to higher frequency of late reactions. Because of advantages associated with dosimetric parameters of proton therapy compared with IMRT and F-SBRT, this therapy is used for reirradiation treatment with aim to reduce treatment-related toxicity and to protect previously irradiated healthy tissues. So far only several studies have been published involving

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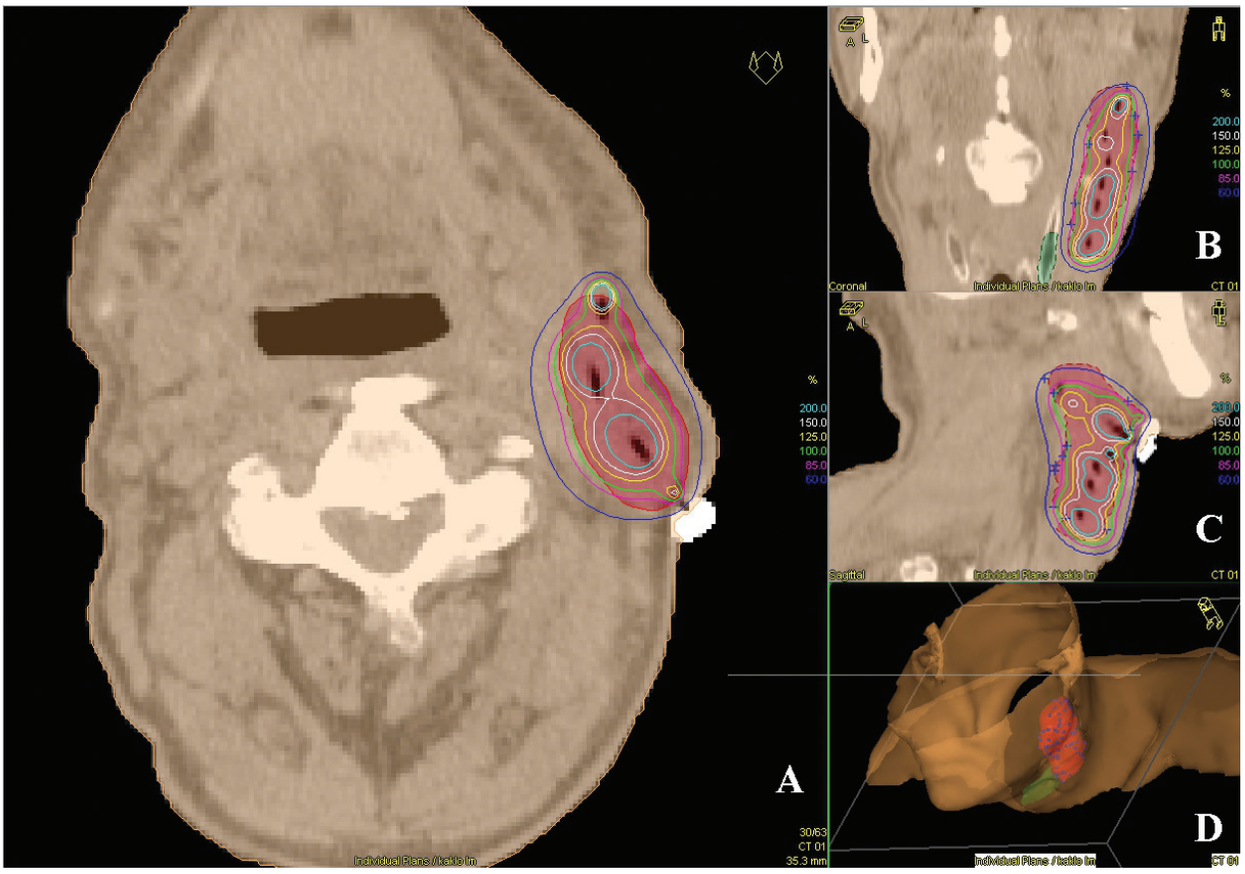


Figure 3. HDR-BRT dosimetric plan shown on axial (A), coronal (B) and sagittal (C) CT slice, 3D view of PTV (red) (D) for a patient with isolated neck recurrence of tonsil squamous cell carcinoma. PTV volume was 37.85 cm^3, V100 = 85.89%, V150 = 32.28%, V200 = 12.1%, HI = 0.62, DNR = 0.37.

application of proton beam therapy to treat head and neck cancer relapse. Romesser et al. published results of a multi-institutional study during which 92 patients were treated using proton beam therapy [36]. Median follow-up was 13.3 months (range 8.2–19.2 months) for surviving patients, and 10.4 months for all patients (range 5.3–17.5 months). In total, 65 (70.7%) men and 27 (29.3%) women were included in this study with a median age of 63 years (range 51.5–70 years); 70.7% of patients had Karnofsky Performance Score 80 and higher. Median time between initial radiotherapy and proton beam therapy was 34.4 months (range 8.2–19.2 months). Study subject group was very heterogeneous according to tumor localization: oropharynx—17 (18.5%), nasal cavity and paranasal sinuses—12 (13%), larynx or hypopharynx—10 (10.9%), salivary glands—11 (12%) and nasopharynx—9 (9.8%); also, there were included five patients with skin, eight patients with skull base tumors and eight patients diagnosed with tumors in other locations. Most of subjects—52 (56.5%)—had histologically confirmed diagnosis of squamous cell carcinoma. Prior to proton beam therapy, 36 (39.1%) patients received surgical treatment; median prescribed dose was 60.6 Gy (range 50–66.1 Gy). About 44 (47.8%) patients received concurrent biological therapy based on cetuximab. The 12-month regional control was 25.1%; skull base was the most frequent location of local recurrence. The 12-month overall survival reached 65.2%, freedom-from-distant metastasis was 84%. Late grade 3 and higher toxic skin reactions and dysphagia were diagnosed in six (8.7%)

and four (7.1%) patients, respectively, two (2.9%) patients were diagnosed with treatment-related bleeding (grade 5 toxicity). Phan et al. used proton beam therapy to treat 60 patients, including 55 diagnosed with head and neck cancer relapse and five diagnosed with secondary tumor [37]. Largest segment (16 patients) consisted of recurrent oropharyngeal tumors, five nasopharyngeal tumors, 11 sinonasal tumors, eight parotid gland tumors. A total of 40 (66.7%) patients had histologically confirmed squamous cell carcinoma; median time between initial radiation therapy and proton beam therapy was 47.1 months (range 7.3–438.2 months), median follow-up was 13.6 months (range 0–50 months). A total of 35 (58%) patients received surgical treatment, 44 (73%) received proton beam therapy in combination with chemotherapy. Median prescribed dose of adjuvant proton beam therapy was 61.5 Gy (range 50–70 Gy); in patients who received a definitive PBRT median dose was 66 Gy (range 50–70 Gy). The 1-year and 2-year locoregional control was 68.4% and 55.9%, overall survival—81.3% and 69%, progression-free survival—60.1% and 48.2%, distant metastasis-free survival—75% and 63.7%, respectively. Frequency of late grade 3 toxicity was 20% (12 patients); no grade 4 toxicity was diagnosed, yet death of two (3%) patients was potentially treatment related.

PBRT is an effective treatment method for patients diagnosed with head and neck cancer relapse; however, results of this treatment method are difficult to compare with other radiotherapy regiments (**Table 3**). Study groups were highly heterogeneous according to the primary tumor location, different cancer types have been included (squamous cell carcinoma, sarcoma, adenocarcinoma, etc.), part of patients received surgical treatment before proton beam therapy, others received combined chemotherapy or biological therapy. It is therefore necessary to conduct further studies with aim to assess advantages of proton beam therapy compared with IMRT or F-SBRT.

Recommendations for PBRT:

1. Proton beam therapy is recommended for patients with good functional status, deciding individually and comparing treatment planning dosimetric parameters of PBRT and IMRT or F-SBRT to each other.
2. Proton beam therapy is recommended for patients if relapse volume does not exceed 50 cm^3.

Author	N	Treatment	Late toxicity grade 3–4	Results
Romesser et al. [36]	92	(a) Surgery+PBRT (n = 36) (b) Biological therapy+PBRT (n = 44) Median dose 60.6 Gy (50–66.1 Gy)	Dysphagia—7.1%, skin reactions—8.7% grade 5—2.9%	1 y OS—65.2% 1 y DFS—84%
Phan et al. [37]	60	(a) Surgery+PBRT/(n = 35) (b) PBRT+CHT/(n = 44) Median dose 61.5 Gy (50–70 Gy)	20% Grade 5—2.8%	1 y OS—81.3% 2 y OS—69% 1 y LC—68.4% 2 y LC—55.9% 1 y DFS—75% 2 y DFS—63.7%

Notes: PBRT, proton beam therapy; CHT, chemotherapy; OS, overall survival; DFS, disease free survival; LC, local control.

Table 3. Summary of published data on PBRT for recurrent head and neck cancer.

2.4. Organs at risk

2.4.1. Spinal cord and brain stem

In some studies, the cumulative dose limit was ≤60 Gy, delivered in 2 Gy/fraction, 5 days/week (biologically equivalent dose [BED] 120 Gy_2). There were no cases of myelopathy in these studies, and a minimal time interval between primary therapy and reirradiation was 6 months [27, 38, 39]. When applying fractionation regimen of 2 Gy/day, and after irradiating the full cord cross-section to a total dose of 50, 60 and ~69 Gy, the frequency of myelopathy was 0.2%, 6% and 50%, respectively [39]. However, most authors recommend not to exceed the cumulative dose of 50 Gy [19, 24, 26]. When using the hypofractionated stereotactic body radiation therapy, it is recommended not to exceed the cumulative dose of 25 Gy (2 Gy—equivalent dose, $\alpha/\beta = 2$), when the total dose of primary radiotherapy does not exceed 50 Gy and the minimal time between two radiotherapy courses is 5 months [40].

2.4.2. Mandible

Up to this date there are no clear volume and dose limitations when using the reirradiation therapy, although osteoradionecrosis is one of the possible late toxic reactions. Studies published by De Crevoisier et al. and Duprez et al. indicate osteoradionecrosis frequencies of 8% and 3.6%, when administering total cumulative dose of 130 Gy, using conventional radiotherapy [10, 26]. In a research conducted by Salama et al., the total cumulative dose was 135 Gy, and frequency of osteoradionecrosis was 11% [41]. When using repeated stereotactic body radiation therapy in patients who received a total dose of 66–70.2 Gy during the primary radiotherapy, it is recommended not to exceed 25–40 Gy/5 fractions (BED 40–90 Gy_2) [40].

2.4.3. Larynx/hypopharynx

In study conducted by Tanvetyanon et al., frequency of laryngeal toxicities of grade 3 and higher was 7.8%, when administering a total cumulative dose of 124 Gy [21]. Takiar et al. completed a 15-year analysis and published its results, which include: chondroradionecrosis after delivering 140 Gy total cumulative dose; non-healing ulcer and stenosis requiring surgery after ≥120 Gy [42]. It is therefore recommended that the total cumulative dose for larynx and hypopharynx does not exceed 120 Gy.

It is recommended to reduce (according to possibilities) the total dose which involves such organs as base of tongue, carotid arteries, jugular veins, oral cavity, sternocleidomastoid muscle, parotid and submandibular glands; however, there is no dose limit established for these body structures.

3. Conclusions

Reirradiation therapy is suitable and safe method of treatment for patients diagnosed with head and neck cancer relapse. It is important to take into consideration the functional status of the patient, recurrence location and volume, and time interval between initial radiotherapy

and reirradiation. Surgical treatment, chemotherapy or biological therapies are more efficient methods of treatment when combined with reirradiation. Currently there is a lack of randomized clinical trials comparing effectiveness and toxicity of different radiotherapy methods, so for each case the potential of reirradiation therapy must be evaluated individually, considering recommendations presented here.

Author details

Viktoras Rudzianskas* and Rita Kupcinskaite-Noreikiene

*Address all correspondence to: wictoras@hotmail.com

Institute of Oncology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

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