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High-dose-rate and pulsed-dose-rate brachytherapy in palliative treatment of head and neck cancers

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ABSTRACT

PURPOSE: The main purpose of the study was to assess the results of high-dose-rate brachytherapy (HDRBT) and pulsed-dose-rate brachytherapy (PDRBT) in the palliative treatment of patients with locally or regionally recurrent head and neck cancers. The detailed aims concerned the evaluation of these methods in the context of local control, survival, and complications rates in patients subgrouped by different parameters such as age, gender, primary and recurrent tumor localization, tumor size, treatment method (HDR/PDR), primary treatment method, and radiation dose applied.
METHODS AND MATERIALS: PDRBT and HDRBT were used in 106 and 50 patients, respectively. In 8 patients, BT procedures were performed in combination with simultaneous chemotherapy. Sixteen patients were additionally treated with interstitial hyperthermia. All patients were regularly followed up within 6 months. Local control, complications, and survival were assessed. Materials included 156 patients with head and neck cancers treated palliatively with HDRBT and PDRBT in the Department of Otolaryngology of Poznań University of Medical Sciences and in the Department of Brachytherapy of Greater Poland Cancer Center from January 2002 to November 2008.
RESULTS: Complete and partial remissions 6 months after finishing the treatment were achieved in 37.7% of patients, whereas survival rates 12 and 24 months after brachytherapy were estimated for 40% and 17%, respectively. The overall complications rate was 35%.
CONCLUSIONS: Our results suggest that HDRBT and PDRBT constitute a safe alternative in the palliative treatment of patients with locally or regionally recurrent head and neck cancers with a relapse in a previously irradiated area, which were not qualified or rejected surgery. It gives a good palliative effect with acceptable complication rate. © 2012 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: High-dose-rate (HDR) brachytherapy; Pulsed-dose-rate (PDR) brachytherapy; Recurrence; Head and neck cancers; Palliative treatment

Introduction

The patients with recurrent head and neck cancers remain a challenge for oncologists. Treatment options are frequently limited for this group because of the extent of tumor precluding complete resection with clear surgical margins or full dose of external beam radiotherapy (EBRT) applied during first-line therapy. Brachytherapy (BT) can represent a method of choice in such a group. It provides specific intensive local irradiation allowing protection of surrounding structures, preserving organ function, and giving a good palliative effect (1–4).

The main purpose of the study was to assess the results of HDRBT and PDRBT in the palliative treatment of patients with locally or regionally recurrent head and neck cancers. The detailed aims concerned the evaluation of these methods in the context of local control, survival, and complications rates in patients subgrouped by different parameters such as age, gender, primary and recurrent tumor localization, tumor size, treatment method (HDR/PDR), primary treatment method, and radiation dose applied.

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Methods and materials

The analysis includes all patients with head and neck cancers treated palliatively with HDRBT or PDRBT from January 2002 to November 2008 in the Department of Otolaryngology of Poznań University of Medical Sciences and in the Department of Brachytherapy of Greater Poland Cancer Center. The study group consisted of 156 patients, 133 men and 23 women in a mean age of 59 years (age range, 41–89 years). Criteria for eligibility for the treatment were histologically confirmed recurrent nonresectable tumor with no evidence of distant metastases, completion of radiation therapy (when accepted and safe), and availability for BT techniques. Most patients (142 patients, 91%) were previously irradiated with curative intent and a full dose of EBRT. They were disqualified for second EBRT because of enhanced risk of radionecrosis. In 14 cases, EBRT had not constituted a part of the treatment because of the lack of patient consent (8 patients), connective tissue disorders (2 patients), cancer cachexia (2 patients), and claustrophobia (2 patients). Most patients had advanced stage tumor at the time of admittance. Recurrences were mostly located in cervical lymph nodes. Squamous cell carcinoma dominated. The patient characteristics are presented in Table 1.

Table 1
Patient characteristics

	Number (percentage) of patients, *n* (%)		
		Method of treatment	
Characteristic		Pulsed-dose-rate brachytherapy	High-dose-rate brachytherapy
Age	Median, 59 y		
<59	82 (52.6)		
≥59	74 (47.4)		
Gender			
Male	133 (85.2)		
Female	23 (14.8)		
Primary tumor localization			
Larynx, hypopharynx	72 (46.2)	53 (73.6)	19 (26.4)
Larynx	37 (23.7)		
Hypopharynx	12 (7.7)		
Larynx, hypopharynx	23 (14.8)		
Floor of mouth/tongue	40 (25.6)	23 (57.5)	17 (42.5)
Oropharynx	27 (17.3)	18 (66.7)	9 (33.3)
Paranasal sinuses	6 (3.8)	3 (50)	3 (50)
Carcinoma of unknown primary	5 (3.2)	4 (80)	1 (20)
Salivary glands	4 (2.6)	4 (100)	—
Nasopharynx	2 (1.3)	1 (50)	1 (50)
Histopathology			
Squamous cell carcinoma	145 (93)		
Solid carcinoma	3 (1.9)		
Cylindroma	2 (1.3)		
Lymphoma/squamous cell carcinoma	2 (1.3)		
Lymphoepithelioma	2 (1.3)		
Malignant melanoma	1 (0.6)		
Oncocytoma	1 (0.6)		
Primary treatment			
Surgery, radiotherapy	101 (64.7)		
Radiotherapy	25 (16)		
Surgery	12 (7.7)		
Surgery, radiotherapy, chemotherapy	10 (6.5)		
Radiotherapy, chemotherapy	6 (3.8)		
Surgery, chemotherapy	2 (1.3)		
Recurrent tumor localization			
Cervical lymph nodes	84 (54.2)	65 (77.4)	19 (22.6)
Oropharynx	43 (27.6)	21 (48.8)	22 (51.2)
Tracheostomy region	22 (14.1)	16 (72.7)	6 (27.3)
Paranasal sinuses	4 (2.6)	2 (50)	2 (50)
Salivary glands	2 (1.3)	2 (100)	—
Nasopharynx	1 (0.6)	—	1 (100)
Tumor size			
<2 cm	10 (6.5)		
2–4 cm	44 (28.2)		
>4 cm	102 (65.3)		

PDRBT and HDRBT were used in 106 and 50 patients, respectively. There were no specific criteria for eligibility for PDR or HDR technique. The choice was mainly conditioned by organizational arrangements (the need for hospitalization in PDRBT) and by the general patient condition (long-term immobilization during PDRBT). Most patients had sole BT. In 8 patients, BT procedures were performed in combination with simultaneous chemotherapy—such a small percentage resulted from the limited availability of that form of therapy, from the patient's general condition and their lack of consent for such a modality. Sixteen patients were additionally treated with interstitial hyperthermia (microwaves 915 MHz; BSD Medical 500, BSD Medical Corp., Salt Lake City, UT, USA). Hyperthermia was used in 13 patients with extensive recurrence in cervical lymph nodes and in 3 patients with advanced recurrence in tracheostomy or oral region. PDR catheters were implanted in the Department of Otolaryngology—under general anesthesia, after description of the target volume (clinical examination, CT scans/MRI imaging, intraoperative image, and intraoperative ultrasonography), parallelly with a constant distance of 1–1.5 cm to achieve homogenous dose distribution, with a margin of 15–20 mm. HDR catheters were prepared in the Department of Brachytherapy. In one case of a nasopharyngeal cancer, intracavitary BT was applied.

All patients were given antibiotics preventively. The proper treatment started 1–7 days after applicators insertion, preceded by precise planning that was undertaken in the Department of Brachytherapy. CT-based treatment planning was performed for all interstitial implants to calculate the dose distribution to the target volume and adjacent healthy tissues. Plans were optimized using standard geometric optimization, and prescription dose was based on the modified Paris dosimetry treatment. Target volume was in most cases 5 mm beyond the gross tumor volume. It was delineated after taking into account all relevant structures such as carotid vessels or spinal cord. Example of treatment plan is presented on Fig.1a and b. Isodose plots were generated to evaluate the plan. PDRBT and HDRBT were applied in compliance with European recommendations, using the following equipment (Nucletron BV, Veenendaal, The Netherlands): Integrated Brachytherapy Unit, PLATO or Oncentra planning system and microselectrons PDR and HDR with iridium-192 sources used for treatment delivery.

The total dose of PDRBT for all patients ranged from 20 to 40 Gy (median, 20 Gy). A dose per pulse in a median value of 0.7 Gy (range, 0.6–0.8) was prescribed. It corresponded to the reference dose, which was prescribed at 85% of the mean central dose. The pulses were delivered in 20–24 hours with a time interval of 1 hour between the pulses. HDRBT was delivered twice a day with intervals of at least 6 hours. Median total dose ranged from 12 to 30 Gy given in 3 to 10 fractions, 3–6 Gy per fraction in 2–5 days.

All patients were regularly followed up: 1 month after treatment and then every 3 months. Detailed followup concerned the period of 6 months after finishing the treatment.

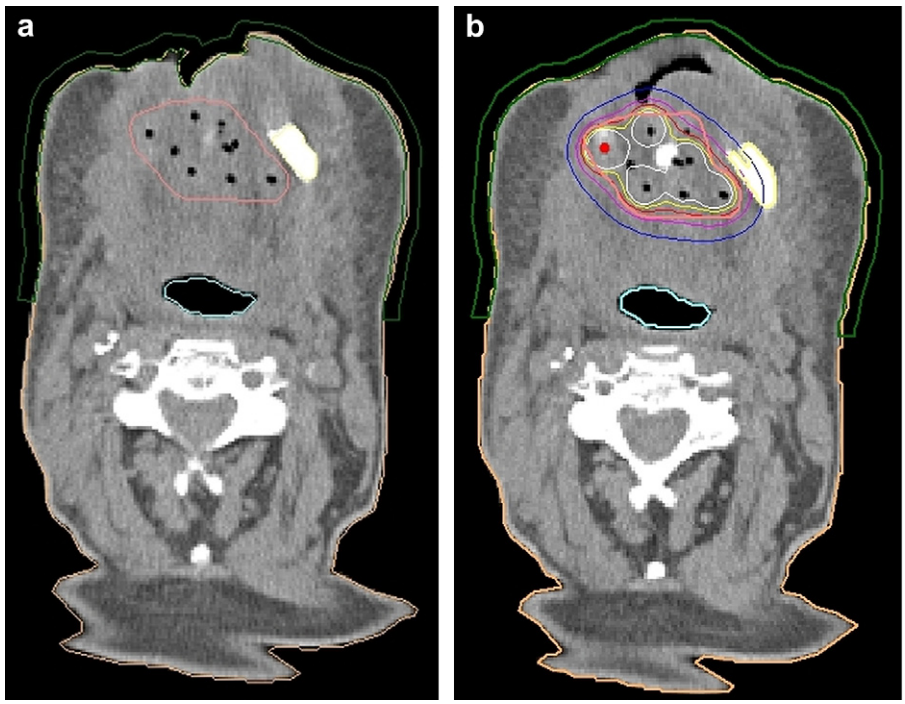

Fig. 1. (a) Example of recurrent tongue and floor of the mouth cancer; nine interstitial applicators (blind-end, Nucletron) visible clinical tumor volume is selected and stroked. (b) Treatment plan with isodoses; red line means 100% of prescribed dose and blue isodose presents 50% of dose. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Data on survivals mostly came from indirect sources (correspondence and phone contact). The local control was assessed by the clinical examination and imaging techniques if required. The five-grade scale was used to describe the local status: (*1*) complete remission (CR), (*2*) partial remission (PR), (*3*) nonremission, (*4*) progression, and (*5*) death. The complications were noted as well. They were classified as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life threatening/disabling (Grade 4), or leading to death (Grade 5) (Common Terminology Criteria for Adverse Events v3.0, National Cancer Institute, 2006).

Kaplan–Meier method was used to generate survival estimates. Local control was based on the number of months between the first day of treatment to the date of locoregional progression. For censored patients, the last date of progression-free followup was used in the survival estimates. Overall survival was based on the number of months between the first day of brachytherapy to the date of death or the last date of followup for censored patients.

Results

CR and PR 6 months after finishing the treatment were achieved in 37.7% of patients. In Table 2, local control rates 4 weeks, 3 and 6 months after finishing brachytherapy are presented, whereas in Table 3 local control rates 6 months after finishing the treatment in different recurrent tumor localizations are presented.

The mean overall survival was 8 months (range, 1–48 months; median, 7 months). According to the Kaplan–Meier method, the 12-month and 2-year survivals were estimated for 40% and 17%, respectively (Fig. 2). In 18 patients (11.5%), metastases occurred—14 developed neck metastases and the other four distant metastases. 87.2% of patients died of tumor progression, and 12.8% died of other causes, although apparently free of disease (liver failure, cardiac failure, pulmonary embolism, complications of treatment, and diagnosis of the second tumor). Statistically significant differences were not found in response to treatment in patients subgrouped by different parameters such as age, gender, recurrent tumor localization, tumor size, treatment method (HDR/PDR), and primary treatment method. The only correlation was found between the local control rate and primary tumor localization—the carcinomas of unknown primary response to treatment were worse than in other sites ($p = 0.015$). The application of hyperthermia also did not have a significant influence on the therapy results.

Table 2
Local control rates at 4 weeks, 3 months, and 6 months posttreatment

	Number (percentage) of patients, *n* (%)		
Result	Local control rate after 4 weeks	Local control rate after 3 months	Local control rate after 6 months
CR	26 (16.6)	26 (17.1)	27 (19.7)
PR	79 (50.5)	65 (41.5)	25 (18)
NR	16 (10.2)	13 (8.5)	0 (0)
Progression	34 (21.7)	34 (21.9)	47 (34.4)
Death	1 (1)	17 (11)	39 (27.9)

CR = complete remission; PR = partial remission; NR = nonremission.

The overall complications rate was 35%. The acute ones mostly included mucositis (60.3% of all patients and 42.3% of Grade 1, 10.9% of Grade 2, and 7.1% of Grade 3 according to Common Terminology Criteria for Adverse Events v3), pain (19.8% of cases; 16% of Grade 2, and 3.8% of Grade 3), and dysphagia (16% of all patients and 14.1% of Grade 2 and 1.9% of Grade 3). Late complications occurred in 25 patients: 24 patients (15%) developed soft-tissue necrosis (Grade 2), whereas 1 patient developed osteoradionecrosis. The complications occurred statistically more often in older patients ($p = 0.025$); they were noted in 21% of patients below the mean age (59 years) and in 38% of patients under that borderline. There was no correlation between the occurrence of local complications and the applied radiation dose. Gender, primary tumor localization, recurrent tumor localization, tumor size, treatment method (HDR/PDR), and primary treatment method had no influence on the development of complications as well.

Discussion

Local or regional recurrences after first-line therapy are one of the most severe problems in the treatment of head and neck squamous cell carcinomas. Curative therapeutic options for this patient group are limited. Unfortunately, there are no well-defined guidelines for selecting patients for salvage treatment. In most cases, the decision is based on the individual clinician's preferences, on the patient's general condition and their desire for further therapy, or on the availabilities of certain forms of therapy. However, if the tumor is left untreated, the prognosis and the quality of life are quite poor with a median survival of only 5 months (5). Chemotherapy is widely used as a salvage alternative but generally gives a response rate <50% with a median survival of 5–8 months (6, 7), and survival advantages are seen only in complete responders (8). Reirradiation has been an unpopular therapeutic option in the past because of concerns about normal-tissue toxicity. However, in recent studies, this potentially high incidence of tissue complications is not seen (9, 10). The combination of chemotherapy with reirradiation seems to be the best treatment modality and is associated with the greatest absolute survival benefit of 8% (11). Unfortunately, it is limited by its toxicity (12–14).

Brachytherapy has gained actuality in the treatment of recurrent or advanced head and neck cancers. Most published results concern low-dose-rate techniques, which have still been being replaced by more flexible and safer modalities (15, 16). In English literature, there are only few articles regarding both HDR and PDR methods in the treatment of relapses in head and neck area. In that summary,

Table 3
Local control rates 6 months posttreatment in different recurrent tumor localizations

Recurrent tumor localization	Number of patients	CR	PR	NR	Progression	Death
		Number (percentage) of patients, *n* (%)				
Cervical lymph nodes	72	17 (23.6)	20 (27.8)	—	10 (13.9)	25 (34.7)
Oropharynx	39	7 (17.9)	2 (5.1)	—	20 (51.3)	10 (25.7)
Tracheostomy region	20	1 (5)	3 (15)		12 (60)	4 (20)
Paranasal sinuses	4	—	—	—	4 (100)	—
Salivary glands	2	1 (50)	—	—	1 (50)	—
Nasopharynx	1	1 (100)	—	—	—	—

CR = complete remission; PR = partial remission; NR = nonremission.

we would like to follow these articles in terms of results and compare them with the own findings.

In most articles, local control rates 2 years after finishing salvage brachytherapy remain at the level of 40%–50%. However, we can also find publications presenting more optimistic results—even 80% of CRs (17–19). Similarly, different data concerning survival rates are presented—the 2-year survival rates range from 35% to even 80%. It is undoubtedly because of the heterogeneity of the groups that are analyzed and in most cases requires descriptive interpretations. In our group, CR and PR 6 months after finishing the treatment were achieved in 37.7% of patients, whereas survival rates 12 and 24 months after brachytherapy were estimated for 40% and 17%, respectively.

Glatzel et al. (20) treated 51 patients with recurrent head and neck cancers with HDRBT, achieving local control at 2 years in 28% of patients and median survival of 6 months. Donath et al. (21) in the similar group obtained local control in 19% of patients. Hepel et al. (22) treated with brachytherapy 70 head and neck patients with a relapse in a previously irradiated area, who were not qualified or rejected surgery. Forty-three percent of patients were simultaneously administered chemotherapy, 36% were additionally treated with hyperthermia, and 6% with EBRT. Local control rate after 12 months was 69%, with the median survival at the level of 56%. The authors observed different response to treatment in various relapse localizations—nasopharynx, 100%, local control rate; for the neck, 67%; for the anterior part of the tongue, 57%.

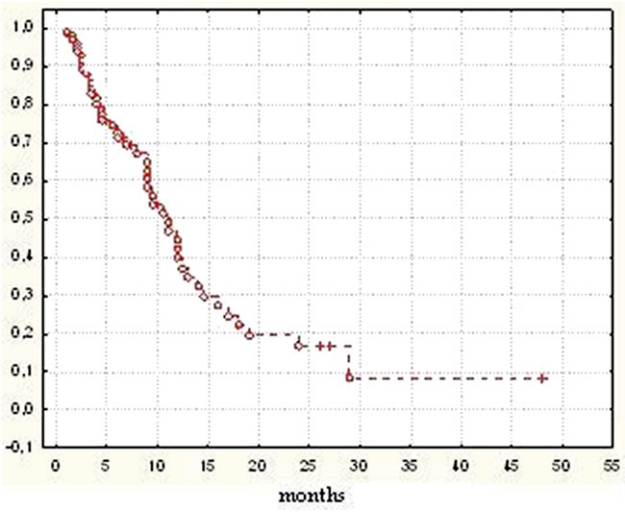

Fig. 2. Survival rate according to Kaplan–Meier method.

In the literature, there are only a few articles concerning the subject of connecting brachytherapy with hyperthermia in the treatment of head and neck cancers. Emami et al. (23) used that associated method in the group of 45 patients with the tumor relapses and compared the results with those achieved in the group of 40 patients treated with brachytherapy solely. Response to treatment was better in the first group (CR: 62% vs. 52%); however, the results were not statistically significant. We also did not observe the correlation between the method of treatment (BT vs. BT + hyperthermia) and local control rates ($p = 0.586$).

In the evaluation of the usefulness of the procedure, we should consider a scale of complications it is associated with. According to the literature, brachytherapy brings similar percentage of early undesirable effects as EBRT. Some authors even emphasize the fact that carefully planned BT can lead to fewer complications than EBRT (24–26). In most articles, the percentage of HDR and PDR complications ranges between 5% and 40%. In our group, it came to 35%.

The most often early complications of HDR brachytherapy combined with surgical treatment are impaired wound healing, transplant necrosis, soft-tissue necrosis, and fistulas, whereas among late undesirable effects osteoradionecrosis and intensified fibrosis are mentioned (27). Soft-tissue necrosis relates to 2% to 45% of patients treated with brachytherapy. It appears more often in HDR (5%–45%) (27–29) than in PDR (2%–13%) method (30–34). In the literature, similar data concerning osteoradionecrosis can be found; it occurs in 6%–38% of HDR patients and in about 3%–8% of those dealing with PDR technique (27, 29,34–37). In our group, soft-tissue necrosis was noted in 15% of all patients, whereas osteoradionecrosis occurred in only one patient. Such a low percentage of late complications can be explained by a relatively short followup. Among all, undesirable effects requiring medicines or surgery mucositis was observed most often—moderate or severe radiation-induced reactions concerned 18% of all patients. Comparable results are presented by Strnad et al. (33), de Pree C et al. (30), and Patra (37). One of the aims

of the study was looking for the factors influencing complication rate. The only correlation was found in case of age; the complications occurred statistically more often in older patients ($p = 0.025$): they were noted in 21% of patients below the mean age and in 38% of patients under that borderline. There was no correlation between the occurrence of local complications and treatment method (HDR/PDR), although literature suggests that they occur more often in HDR technique. It can indicate carefully selected parameters such as total dose, fraction dose, and treatment time in HDR method. Similar conclusions are shown by Levendag et al. (38). Kakimoto et al. (39) were trying to compare LDR and HDR techniques, the percentage of soft tissue and bone necrosis stayed at the same level in both methods.

Conclusions

Our results suggest that HDRBT and PDRBT can be safely used in the palliative treatment of patients with locally or regionally recurrent head and neck cancers with a relapse in a previously irradiated area, which were not qualified or rejected surgery. It gives a good palliative effect with acceptable complication rate.

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