

Is there a place for brachytherapy in the salvage treatment of cervical lymph node metastases of head and neck cancers?

Anna Bartochowska^{1,*}, Janusz Skowronek^{2,3}, Malgorzata Wierzbicka¹,
Malgorzata Leszczynska¹, Witold Szyfter¹

¹Department of Otolaryngology—Head and Neck Surgery, Poznan University of Medical Sciences, Poznan, Poland

²Brachytherapy Department, Greater Poland Cancer Center, Poznan, Poland

³Electroradiology Department, Poznan University of Medical Sciences, Poznan, Poland

ABSTRACT

PURPOSE: Therapeutic options are limited for unresectable isolated cervical lymph node recurrences. The purpose of the study was to evaluate the feasibility, safety, and efficacy of high-dose-rate (HDR) and pulsed-dose-rate (PDR) brachytherapy (BT) in such cases.

METHODS AND MATERIALS: Sixty patients have been analyzed. All them had previously been treated with radical radiotherapy or chemoradiotherapy with or without surgery. PDR-BT and HDR-BT were used in 49 and 11 patients, respectively. In PDR-BT, a dose per pulse of 0.6–0.8 Gy (median 0.7 Gy) was given up to a median total dose of 20 Gy (range, 20–40 Gy). HDR-BT delivered a median total dose of 24 Gy (range, 7–60 Gy) in 3–10 fractions at 3–6 Gy per fraction.

RESULTS: The overall survival and lymph node control rates at 1 and 2 years were estimated for 31.7% and 19%, and 41.4% and 27.3%, respectively. Serious late side effects (soft tissue necrosis) were observed in 11.7% of patients. Adverse events occurred statistically more often in patients >59 years ($p = 0.02$).

CONCLUSIONS: HDR-BT and PDR-BT are feasible in previously irradiated patients with isolated regional lymph node metastases of head and neck cancers. The techniques should be considered if surgery is contraindicated. They provide acceptable toxicity and better tumor control than chemotherapy alone. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords:

PDR brachytherapy; HDR brachytherapy; Neck recurrence; Head and neck cancers; Salvage treatment

Introduction

Isolated cervical lymph node recurrences occur in approximately 10% of patients after radical irradiation of squamous cell carcinoma of the head and neck. Although surgical salvage is the preferable treatment for this population, it is not feasible in at least one-third of cases (1). For patients with unresectable nodal tumor, the current standard

treatment is concurrent chemoradiation (2). However, chemotherapy is of limited benefit when administered as a single modality and provides median survival of only 6 months (3). On the other hand, because of considerable toxicity, full-dose reirradiation cannot be implemented in most previously irradiated patients. Is there a place for brachytherapy (BT) in such cases?

In the literature, minimal data exist regarding the treatment of regional neck metastases with the interstitial BT. Moreover, most of them are presenting results of low-dose-rate (LDR) techniques which have been replaced by more adaptable and safer modalities (4, 5).

The aim of our study was to evaluate the feasibility, safety, and efficacy of interstitial high-dose-rate (HDR) and pulsed-dose-rate (PDR) BT in the salvage treatment of isolated cervical lymph node relapses.

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* Corresponding author. Department of Otolaryngology—Head and Neck Surgery, Poznan University of Medical Sciences, 49 Przybyszewskiego Street, 60-355 Poznań, Poland. Tel.: +4861-8691-387; fax: +4861-8691-690.

E-mail address: annabartochowska@gmail.com (A. Bartochowska).

Methods and materials

Patients

Sixty patients with squamous cell carcinoma neck metastases amenable for salvage surgery treated with interstitial BT have been included into the analysis. Surgery was abandoned due to the infiltration of internal carotid artery or prevertebral fascia in 50 and 4 patients, respectively, while was contraindicated because of anesthetic reasons in six cases. There was no evidence of local recurrence in the primary tumor site nor distant metastatic spread. All patients completed full-dose external beam radiotherapy (EBRT) or chemoradiotherapy more than 6 months before BT. The median time from the end of prior radiotherapy to cervical lymph node relapse was 32 months (range, 7–48 months).

The median age of patients was 59 (range, 36–81 years). In the study group, there were 56 men and 4 women. Primary tumor sites were as follows: larynx and hypopharynx (31 of 60; 51.7%), oropharynx (16 of 60; 53.3%), floor of the mouth/tongue (7 of 60; 11.7%), nasopharynx (1 of 60; 1.7%), and unknown in 5 of 61 (8.2%) patients. Most of the nodal recurrences were localized at the Level II (30 of 60; 50%), whereas the remaining at the Level II and III (25 of 60; 41.7%), Level III (3 of 60; 5%) and Level IV (2 of 60; 3.3%). They were classified as N1, N2a, N2b, N2c, and N3 in 8, 13, 19, 9, and 11 cases, respectively. Patients' characteristics, including previous neck treatment modalities details, are described in Table 1.

Table 1
Patients' characteristics—age, gender, primary tumor site and histopathology, primary treatment, recurrence nodal status

	Number (percent of patients)
Age (y)	Mean—59 years
<59	31 (51.7)
>59	29 (48.3)
Gender	
Male	56 (93.3)
Female	4 (6.7)
Primary tumor site	
Larynx and hypopharynx	31 (51.7)
Oropharynx	16 (53.3)
Floor of the mouth/tongue	7 (11.7)
Unknown primary	5 (8.2)
Nasopharynx	1 (1.7)
Primary tumor histopathology	
Squamous cell carcinoma	60 (100)
Primary treatment	
Surgery and radiotherapy	41 (68.4)
Radiotherapy	11 (18.3)
Radiotherapy and chemotherapy	5 (8.3)
Surgery, radiotherapy, and chemotherapy	3 (5)
Recurrence nodal status	
N1	8 (13.33)
N2	41 (68.33)
N3	11 (18.33)

Methods

The treatment was interstitial BT alone in all cases. Simultaneous chemotherapy had not been administered—due to the limited availability of that form of therapy, the patients' general condition, and their lack of consent for such a modality. PDR-BT and HDR-BT were used in 49 (81.7%) and 11 (18.3%) patients, respectively. There were no specific criteria for eligibility for PDR or HDR technique. The choice was conditioned by general patient state (long-term immobilization during PDR-BT, need for hospitalization in PDR-BT). Catheters (Flexible implant tube 6F, 30 cm, Single-leader, Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) were implanted in the Department of Otolaryngology—under general (36 patients) or local (24 patients) anesthesia, after defining the critical structures and the description of the target volume (clinical examination, CT scans/MRI, intraoperative ultrasonography), in a parallel alignment, with a constant distance of 10–15 mm. An average of 4 (range, 2–6) after-loading catheters were inserted. The proper treatment was introduced in the Department of Brachytherapy 1–2 days after catheters placement. Dose distribution was prepared individually for clinical target volume region using IPSA (Inverse Planning Simulated Annealing) optimization algorithm. Examples of treatment plan are presented on Figs. 1 and 2. The following equipment (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden): IBU (Integrated Brachytherapy Unit), PLATO planning system, and microselectrons PDR and HDR (Nucletron) with ¹⁹²Ir sources were used for treatment delivery. In PDR-BT group, a dose per pulse of 0.6–0.8 Gy (median 0.7 Gy) was given up to a median total dose of 20 Gy (range, 20–40 Gy). The pulses were delivered in 20–24 hours with a interval of 1 hour between the pulses. HDR-BT was applied twice a day with intervals of at least 6 hours. Median total dose was 24 Gy (range, 7–60 Gy) given in three–10 fractions (median 5) at 3–6 Gy (median: 5 Gy) per fraction for 2–5 days.

Followup ranged from 1 to 48 months (median: 12 months). Patients were evaluated 1 month after finishing the treatment and then at 3-month intervals. Lymph node control (LNC) was assessed by the clinical examination and imaging techniques if required. Treatment assessment was based on tumor volume response and defined according to the modified WHO response criteria for solid tumors. Four-grade scale was used to describe local status: (1) complete remission (CR), (2) partial remission (PR), (3) stable disease (SD), (4) progressive disease. LNC was based on the number of months between the first day of treatment to the date of locoregional progression after CR, PR, or SD. For censored patients, the last date of progression-free followup was used in the survival estimates. Overall survival (OS) was based on the number of months between the first day of BT to the date of death or the last date of followup for censored patients. Acute and late toxicities were scored using the Common Terminology Criteria for Adverse Events v3.0.



Fig. 1. CT scan of neck with four implanted interstitial catheters (flexible implant tube 6F, 30 cm, Single-leader, Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) in lymph node recurrence on the left side; 100% isodose covered target—infiltrated lymph nodes (CTV). We can observe rapid dose fall outside CTV; (a) transverse cross-section; (b) transverse cross-section; (c) frontal cross-section (reconstructed); (d) sagittal cross-section (reconstructed). CTV = clinical target volume.

Statistical analysis was carried out using Statistica version 7 (StatSoft, Poland). The actuarial probabilities of LC and OS were calculated according to the Kaplan–Meier method. Comparisons were made using the log-rank or χ^2 method or covariance analysis, as appropriate.

The protocol of the investigation has been approved by The Institutional Review Board of the Poznan University of Medical Sciences.

Results

Survival

The median posttreatment OS was 9 months (range, 1–48). According to the Kaplan–Meier method, the OS rates at 1 and 2 years were estimated for 31.7% and 19%, respectively (Fig. 3). Distant metastases occurred in 4 of 60 patients; 93.3% patients died of tumor progression and 6.7% died of other causes, while apparently free of disease (cardiac failure, complications of treatment, diagnosis of the second tumor).

Lymph node control

Complete (CR) and partial (PR) responses 1 month after completion of treatment were observed in 40 of 60 patients,

of which 20% had achieved CR. In 14 of 60 cases, progression of the disease (23.3% of patients) was noted. LNC 6 months after finishing the treatment was 43.9%. The overall LNC probability at 1 and 2 years after the treatment was estimated for 41.4% and 27.3%, respectively (Fig. 4).

Toxicity

The overall complications rate was 50%. Early adverse events occurred in 28 patients and were limited to local infection, hematoma, and mucositis (33.3% of all patients; 20%, Grade 1; 10%, Grade 2; and 3.3%, Grade 3). Serious late side effects were seen in 7 (11.7%) patients who developed soft tissue necrosis (Grade 2)—in six cases, the wounds healed by granulation, and in one case, further surgical treatment was necessary. There were no dosimetric predictions of toxicity in this group of patients. No carotid blowouts or massive hemorrhage during implantation or thereafter was seen.

Statistical analysis of prognostic factors

There were found no statistically significant differences in response to treatment and overall disease survival in patients subgrouped by different parameters such as age, gender, recurrent tumor size, treatment method (HDR-BT/

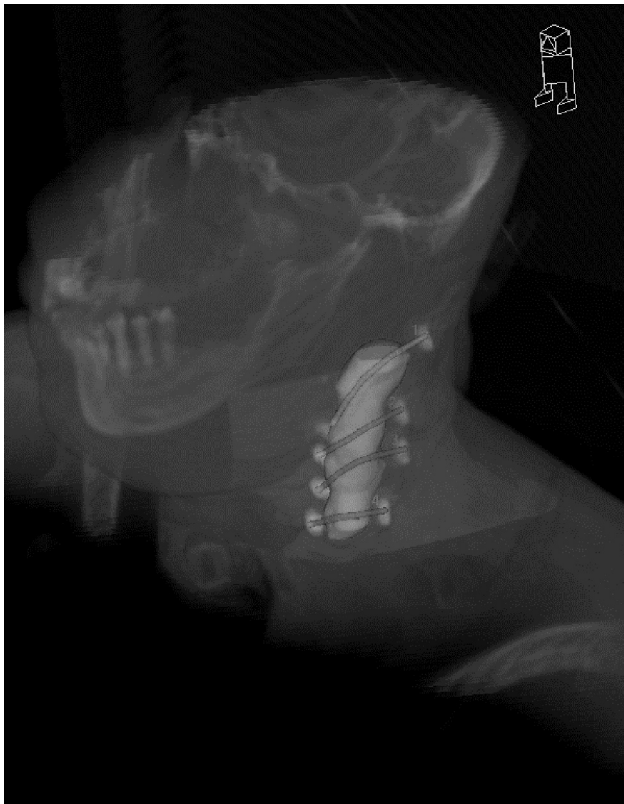


Fig. 2. Digitally reconstructed 3D radiograph—four interstitial catheter visible with radiopaque buttons, clinical target volume (CTV) presented in whitish.

PDR-BT), dose of radiation delivered, and primary treatment method. There was no correlation between the occurrence of local complications and the applied radiation dose. The adverse events occurred statistically more often in older patients (>59 years; $p = 0.02$)—the multivariate analysis did not reveal the higher comorbidities rate in that cohort. Gender, primary tumor localization, tumor size, treatment method (HDR/PDR), primary treatment method, body mass index had no influence on the development of complications as well.

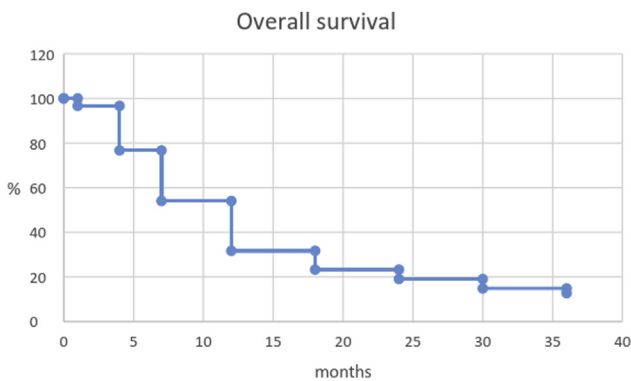


Fig. 3. Kaplan–Meier curve for overall survival.

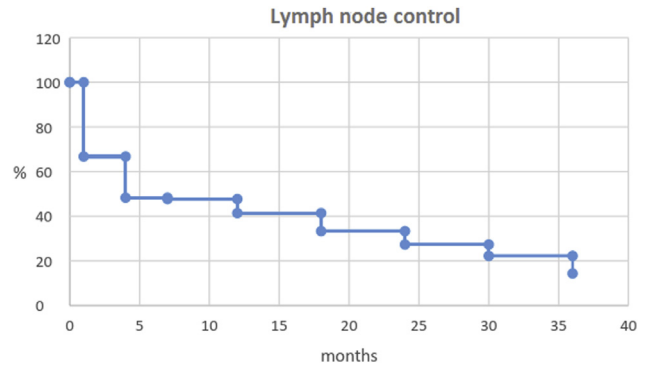


Fig. 4. Kaplan–Meier curve for lymph node control.

Discussion

In worldwide literature, only few reports deal with the salvage BT management of isolated neck lesions developing within previously irradiated volumes. There is especially a lack of clinical data on the role of exclusive BT in the treatment of such tumors. Indeed, most regional head and neck cancer metastases seem to be not appropriate candidates for BT due to the large volumes and not technically accessible infiltration extension or bone invasion (6, 7). The American Brachytherapy Society emphasizes the importance of meticulous implant technique, adequate doses, and larger margins in BT treatment of recurrent head and neck tumors, especially if additional EBRT is not applied (8). For each patient, a balance must be achieved between the probability of LC and possibility of cure, and the probability of toxic complications, and a potentially fatal outcome as a result of treatment (9, 10). However, the role of reirradiation, in terms of palliation, to improve patients' quality of life should also be considered (10–13).

Kolotas *et al.* (14) assessed the therapeutic results obtained with CT-guided interstitial HDR-BT as exclusive treatment for recurrent neck metastases of head and neck tumors. The accelerated hyperfractionated interstitial HDR-BT (2 × 3.0 Gy/d) delivered 30 Gy in 37 of 49 (75%) and 36 Gy in 12 of 49 implants (25%). After 19 months of median followup, the LC rate was 69% and a total of 15 of 49 patients (30%) experienced local disease progression. Of these, nine (18%) had locoregional progression and six (12%) progression within the treated volume. The median post-BT survival was 14 months. The OS rate was 52% at 1 year, 31% at 2 years, and 6% at 3 years. In another study, Tselis *et al.* (15) analyzed 74 patients treated exclusively with HDR-BT for inoperable recurrent cervical lymphadenopathy. The overall and disease-free survival rates at 1, 2, and 3 years were 42%, 19%, and 6% and 42%, 37%, and 19%, respectively. The LC probability at 1, 2, and 3 years was 67% at all three time points. Grades III–IV complications occurred in 13% of patients. Comparing the last series with the results presented by the authors, regarding the effectiveness (2-year OS rate

19%) and the side effects rate (serious late complications 11.7%), the outcomes are quite comparable (although LNC rates are lower—27.3% vs. 67% at 2 years).

Bollet *et al.* (4) treated 84 patients with neck recurrences either with ^{192}Ir LDR-BT alone (72 patients) or in combination with EBRT (12 patients). The majority had relapsed in sites of previous EBRT. The regional control rates in the neck and OS rates were 31% and 13% at 3 years and 0% and 1% at 5 years, respectively, and showed a significant impact of the interval from previous radiotherapy and the applied salvage dose on survival. LNC was better for patients who received total salvage dose >60 Gy (0% vs. 56% at 3 years, $p = 0.0004$) and for those who had achieved initial control for >18 months before relapse (0% vs. 13% at 3 years, $p < 0.0002$). The authors of the present study did not find such correlations. In the Discussion section, Bollet *et al.* conclude that surgery should be a part of any salvage attempt to treat isolated lymph node relapses of head and neck squamous cell carcinomas, in view of the poor results obtained by interstitial BT alone. In the series presented by the authors, surgery was abandoned due to the infiltration of internal carotid artery or prevertebral fascia in most patients. This fact may explain such unsatisfactory results achieved in the study. Puthawala *et al.* (16) evaluated the long-term tumor control of 118 patients with recurrent neck disease. Fifty-three of them had recurrent disease at both the primary site and in the neck, whereas 9 patients were treated for bilateral metastatic neck disease. The salvage BT consisted of a ^{192}Ir LDR-BT, which delivered a median minimum tumor dose of 53 Gy to a mean tumor volume of 68.75 cm². In most cases, hyperthermia and/or chemotherapy were used as a radiosensitizing and potentiating agents. At a minimum 6-month followup, LC was achieved in 74% of patients, whereas 5-year disease-free survival was estimated for 23%. Severe late complications occurred in 18% of patients.

There is no doubt that salvage surgery and perioperative BT are feasible and effective (6). Kupferman *et al.* (5) studied the potential benefit of surgical salvage with interstitial BT in recurrent regional lymph node metastases. Twenty-two patients, all treated with EBRT before recurrence, have been evaluated. All them underwent salvage neck dissection with concomitant BT thereafter. The tumor bed was treated to a median dose of 60 Gy. To avoid significant wound complications among patients with early recurrences after EBRT, the authors limited the BT dose. If the tumor was resected off of the carotid artery, then the catheters were placed directly across the carotid. The median time to regional recurrence after salvage neck dissection and BT was 19 months. The 2-year actuarial regional control rate was 67%, whereas overall actuarial 1-year, 2-year, and 5-year survival rates were 82%, 57%, and 46%, respectively. Pellizzon *et al.* (17) evaluated the long-term results of a treatment policy combining salvage surgery and interstitial HDR-BT for cervical head and neck cancers

recurrences. The crude LC rate for 21 analyzed patients was 52.4%. The 5- and 8-year overall and local relapse-free survival rates were 50%, 42.9%, 42.5%, and 28.6%, respectively. The only predictive factor associated with overall and disease-free survival was negative margin status ($p = 0.0007$ and $p = 0.0002$). The authors concluded that complete surgery was mandatory for long-term control and the doses given by BT were not high enough to compensate for microscopic residual disease after surgery.

In recent years, the practice of full-dose reirradiation has come forward as an option and literature data indicate that with the use of external beam reirradiation durable disease control in about 10% of patients with unresected tumors and in 20% of those with resected tumors can be obtained (2, 18). Stojan *et al.* (19) concluded that reirradiation, administered either with or without concurrent systemic therapy, is feasible and tolerable in properly selected patients with recurrent or a new primary tumor in a previously irradiated area of the head and neck, offering a meaningful survival (in the range of 10–30% at 2 years). Rudžianskas *et al.* (20) compared the efficacy and toxicity of the three-dimensional conformal radiotherapy (3D-CRT) and HDR-BT in the treatment of recurrent head and neck cancer. The OS and LC rates of patients treated with HDR-BT at 2 years were 67% and 63%, whereas in 3D-CRT group 32% and 25%, respectively ($p = 0.002$; $p < 0.001$). Most patients developed mild to moderate acute mucositis and dermatitis. In the 3D-CRT group, severe late toxicity was determined in 35.5% of patients, and in the HDR-BT group, in 3.1% of cases ($p = 0.001$). HDR-BT was reported a more effective and safer treatment approach. In the present study, serious late side effects were seen in 11.7% of patients—more often than in the group of Rudžianskas *et al.* but still much less often than in the 3D-CRT group.

Analyzing relatively poor results of the study, the question raises about the sense of palliative BT in patients with cervical lymph node recurrences amenable for surgery and EBRT. There are still no well-defined recommendations for selecting patients for such a salvage treatment. In most cases, the decision is made individually. However, we should underline that if the tumor is left untreated, the prognosis and the quality of life are quite poor with a median survival of only 5 months (21). Chemotherapy is widely used as a salvage alternative but generally gives a median survival of only 6 months (3). Reirradiation can be considered in properly selected patients with recurrent tumor in a previously irradiated area of the head and neck, offering a survival of 10–30% at 2 years (19). The combination of chemotherapy with reirradiation seems to be the best treatment modality and is associated with the greatest absolute survival benefit of 8% (22). Unfortunately, it is limited by its toxicity (23). Summarizing all data presented previously, it seems that BT, with a median survival of 9 months and overall serious side effects rate of 11.7%, constitutes a feasible alternative in the treatment of cervical lymph node recurrences amenable for surgery.

Another question concerns possible methods that could be used to improve tumor control results. According to Pons *et al.* (24), the occurrence of massive cancer invasion into the carotid artery should not be a contraindication for surgery. En bloc resection of the carotid artery with revascularization using the superficial femoral artery allows for appropriate control of the cancer and carries an acceptable level of neurologic risk. In the opinion of the authors, the method should be further evaluated in terms of oncologic outcomes.

Conclusions

The results of our study show that HDR-BT and PDR-BT are feasible in previously irradiated patients with isolated regional lymph node metastases of head and neck cancers. The techniques should be considered if surgery is contraindicated. They provide acceptable toxicity and better tumor control than chemotherapy alone.

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