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# The Role of High-Dose-Rate and Pulsed-Dose-Rate Brachytherapy in the Management of Recurrent or Residual Stomal Tumor After Total Laryngectomy

Anna Bartochowska, MD, PhD; Janusz Skowronek, MD, PhD; Małgorzata Wierzbicka, MD, PhD; Małgorzata Leszczyńska, MD, PhD; Witold Szyfter, MD, PhD

**Objectives/Hypothesis:** The main purpose of the study was to assess the role and efficacy of high-dose-rate (HDRBT) and pulsed-dose-rate (PDRBT) brachytherapy in the palliative treatment of recurrent or residual stomal tumor after total laryngectomy.

**Study Design:** We aimed at presenting a series of 22 consecutive patients treated in the Department of Otolaryngology, Head and Neck Surgery of Poznań University of Medical Sciences, and in the Brachytherapy Department of Greater Poland Cancer Center.

**Methods:** In 16 patients PDRBT was used and in six patients HDRBT was used. In three patients, BT procedures were performed in combination with simultaneous chemotherapy. Two patients were additionally treated with interstitial hyperthermia. In 16 patients, surgical cytoreduction of the tumor preceded the catheters placement. In six patients, a second course of BT was performed due to neck metastases. All patients were regularly followed up within 6 months. Local control, complications, and survival were assessed.

**Results:** Complete and partial remissions 6 months after finishing the treatment were achieved in four (20%) patients, while survival rates 24 months after BT were estimated for 22%. Severe late complications occurred in two (9%) patients.

**Conclusions:** The results of our study show that HDRBT and PDRBT are feasible in previously irradiated patients with recurrent or residual stomal tumor after total laryngectomy. They provide acceptable toxicity and good palliative effect.

**Key Words:** HDR, brachytherapy, PDR, laryngeal cancer, stomal recurrence, palliative treatment.

**Level of Evidence:** 4.

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## INTRODUCTION

Stomal recurrence of laryngeal cancer is considered to be one of the most serious complications after total laryngectomy. It constitutes a very difficult therapeutic issue and always requires individualized management. Preoperative tracheotomy, advanced preoperative T- and N-classification, and subglottic invasion have been documented to be major risk factors for the recurrence in stomal region.[1–3] The management of stomal recurrence including chemotherapy, external beam radiation therapy (EBRT), and surgery has been reported as unsatisfactory. Treatment can often only be of a symptomatic and palliative nature.[4–6]

Brachytherapy constitutes a method that has gained actuality in the treatment of recurrent or advanced head-and-neck-cancers. Derived from ancient Greek words for short distance (*brachios*) and treatment (*therapy*), it refers to the therapeutic use of encapsulated radionuclides placed within or close to a tumor. It is an internal radiation therapy that is applied either in a permanent or temporary manner, often through the use of catheters into which the radioactive sources are placed. Because the radiation source is close to or within the target volume, the dose is determined largely by inverse-square considerations, and decreases rapidly as the distance from the applicator increases. Different types of brachytherapy according to the dose rate delivered to the tumor can be distinguished. In the high-dose rate brachytherapy (HDRBT), large doses (>12 Gy/h) can be given within a few minutes. The use of such high-dose rates (1–3 Gy/min) carries a greater ratio of late tissue effects, which in practice can be overcome by careful placement of catheters and by good immobility achievable with very short exposures. Pulsed-dose rate (PDRBT) treatment is a recent brachytherapy modality that combines physical advantages of HDRBT technology (isodose optimization, planning flexibility, and radiation safety) with radiobiological advantages of low-dose-rate brachytherapy (repair advantages). It involves short pulses of radiation (3 Gy/h), which can be utilized

From the Department of Otolaryngology, Head and Neck Surgery (A.B., M.W., M.L., W.S.), Poznań University of Medical Sciences; and the Brachytherapy Department (J.S.), Greater Poland Cancer Center, Poznań, Poland.

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Send correspondence to Anna Bartochowska, MD, PhD, Department of Otolaryngology, Head and Neck Surgery, Poznań University of Medical Sciences, 49 Przybyszewskiego Street, 60-355 Poznań, Poland. E-mail: annabartochowska@gmail.com

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TABLE I.
Patients characteristics – age, gender, histopathology, primary treatment.

| Patient characteristics | Number (%) |
|---|---|
| **Age** | Mean - 59 years |
| < 59 | 11 (50%) |
| ≥ 59 | 11 (50%) |
| **Gender** | |
| Male | 20 (91%) |
| female | 2 (9%) |
| **Histopathology** | |
| squamous cell carcinoma | 22 (100%) |
| **Primary treatment of the laryngeal cancer** | |
| surgery, radiotherapy | 16 (73%) |
| Radiotherapy | 1 (5%) |
| Surgery | 3 (13%) |
| surgery, radiotherapy, chemotherapy | 2 (9%) |

(pulsed) every hour. The source strength is 10 to 20 times lower than that used in HDRBT, and the requirements for shielding are less stringent.

The aim of the study was to evaluate efficacy and toxicity of salvage interstitial high-dose rate and pulsed-dose rate brachytherapy for recurrent or residual stomal tumors. The detailed aims concerned the analysis of local control, survival, and complications rates in patients subgrouped by different parameters such as age, gender, tumor size, treatment method (HDRBT/PDRBT), primary treatment method, and applied radiation dose.

## MATERIALS AND METHODS

The analysis includes 22 patients with stomal recurrence of laryngeal cancer after total laryngectomy. In the study group there were 20 men and 2 women in a mean age of 59 years (age range: 41–79 years). The patients characteristic is shown in Table I.

The evaluation of the risk factors for stomal recurrence shows that in the group of 22 patients, in 11 (50%) emergency preoperative tracheotomy was performed, in 15 (68%) subglottic invasion was noted, in 16 (73%) paratracheal lymph nodes were histologically positive. Three patients (14%) refused supplementary radiotherapy directly after total laryngectomy. Eight patients (36%) underwent salvage laryngectomy after the failure of radiation therapy for glottic cancer.

Criteria for eligibility for the BT treatment were biopsy-proven recurrent nonresectable or residual tumor, completion of radiation therapy (full dose of EBRT), and availability for BT techniques. PDRBT and HDRBT were used in 16 (72,7%) and 6 (27,3%) patients, respectively. There were no specific criteria for eligibility for PDR or HDR technique. The choice was conditioned by organizational arrangements (the need for hospitalization in PDRBT) and by the general patient state (long-term immobilization during PDRBT). In three 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), while in two patients hyperthermia (microwaves 915 Mhz; BSD Medical 500, Salt Lake City, UT) was additionally used. In 16 patients, surgical cytoreduction of the tumor preceded the catheters placement (in 7 patients enlarged cervical lymph nodes from the 3rd and 4th region were additionally dissected). In six patients (who were not salvaged surgically), second course of BT was performed due to neck metastases in the fourth region.

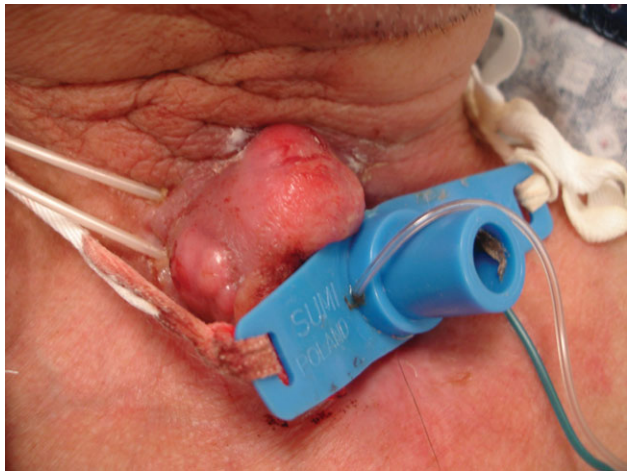

Fig. 1. Stomal recurrence in previously irradiated area, status after laryngectomy, two "blind-end" catheters inserted (Nucletron BV, Veenendaal, Netherlands). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The interstitial catheter placement procedure was performed in the Department of Otolaryngology, Head and Neck Surgery, in the operating room under general anesthesia just after the surgical cytoreduction of the tumor (when applicable). The catheters were implanted after identification of the critical structures and intraoperative defining of the target volume in a parallel alignment, with a constant distance of 10 mm to achieve homogenous dose distribution with a margin of 15 mm (Fig.1). An average of three (range: 2–5) after-loading tubes was inserted. The target volume was also defined postoperatively with the use of CT scans/MRI imaging. The planning target volume (PTV) of BT in our group was in most cases 5 to 10 mm beyond the gross tumor volume (GTV). Plans were optimized using standard geometric optimization, and prescription dose was based on the modified Paris dosimetry treatment. Isodose plots and dose volume histograms were generated to evaluate the plan (Fig. 2–4). Three to five days (median: 4 days) after surgery in the brachytherapy department, the proper treatment

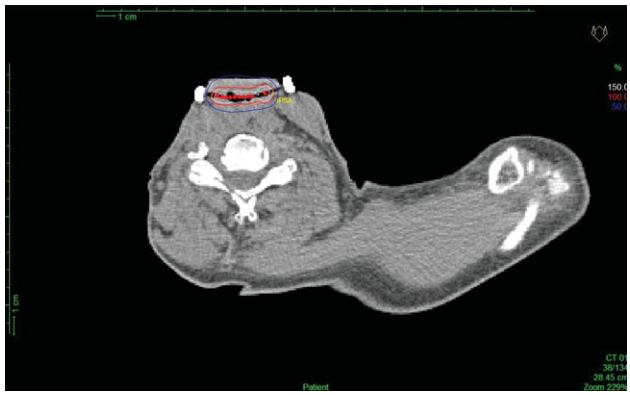

Fig. 2. Transversal section of head and neck region, applicators in tumor with isodoses visible. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

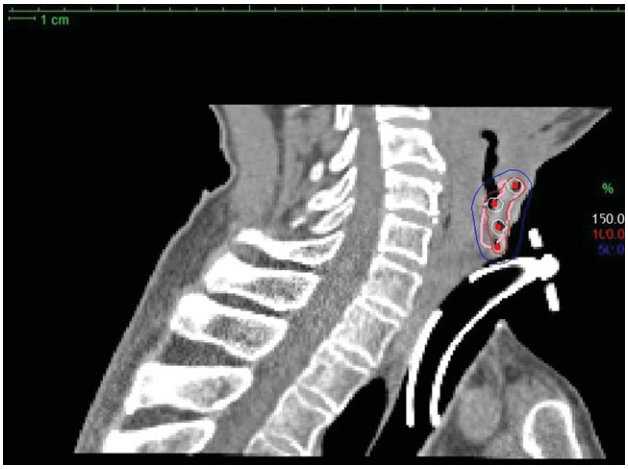


Fig. 3. Sagittal section of head and neck region, four applicators in tumor with isodoses visible. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

started: HDRBT with a median single dose of 5 Gy (range: 3–6 Gy) applied in two daily fractions and a median total dose of 25 Gy (range: 15–48 Gy) or PDRBT with a median value of 0,7 Gy (range 0,6-0,8 Gy) per pulse, and a median total dose of 20 Gy (range: 20–40 Gy) delivered in 20 to 24 hours with a time interval of 1 hour between the pulses. The median treatment time for HDRBT was 3 days (range: 2–5 days) and for PDRBT was 2 days (range: 1–3 days), respectively. Treatment schemes and dose restrictions were individually determined, depending on the tumor location and the proximity to adjacent risk structures. PDRBT and HDRBT were applied in compliance with European recommendations using the following equipment (Nucletron BV, Veenendaal, Netherlands): IBU (Integrated Brachytherapy Unit), PLATO or Oncentra planning system, and microselectrons PDR and HDR with Iridium-192 sources used for treatment delivery.

After completion of BT, all patients were examined 1 month after finishing the treatment and then every 3 months. Detailed follow-up concerned the period of 6 months after finishing the treatment. Data on survivals mostly came from indirect sources (correspondence, phone contact). Local control was assessed clinically and radiographically (ultrasound, MRI, or CT). A complete response (CR) was defined as a complete disappearance of recurrent or residual tumor. A partial response

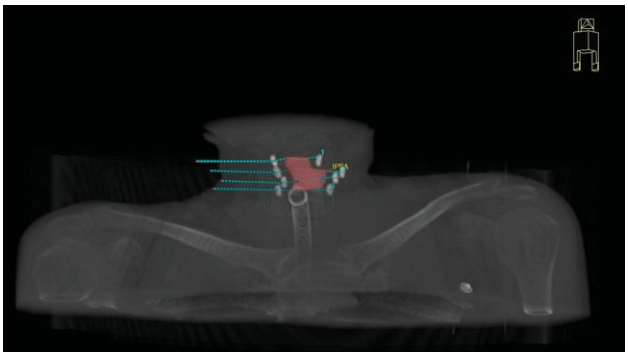

Fig. 4. Example of treatment planning image (Oncentra Planning System, Nucletron BV, Veenendaal, Netherlands) in case of recurrent stomal tumor with four applicators visible. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

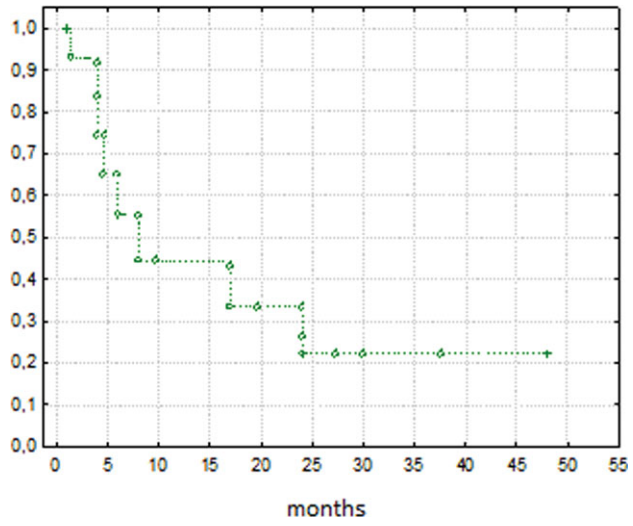


Fig. 5. Overall survival rate according to Kaplan-Meier method. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(PR) was a 50% or more reduction of the tumor diameter. Other responses were scored as no response (NR), stable disease, or progression—at least 25% increase of tumor diameter. Acute and late toxicities were scored using the Common Terminology Criteria for Adverse Events v3.0. They were classified as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening/disabling (4), or leading to death (5). Late toxicity was considered if it had occurred $>$ 3 months after completion of therapy.

Statistical analysis was carried out using Statistica version 7 (StatSoft, Poland). The survival analysis was performed using the Kaplan-Meier method. 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 follow-up 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 follow-up for censored patients.

## RESULTS

The mean survival of the 22 patients was 12 months (range: 2–48 months, median: 9,5 months). According to the Kaplan-Meier method 2-year survival was estimated for 22% (Fig. 5). The overall survival was significantly better for patients receiving salvage surgery as a part of treatment (13 vs. 4,5 months; $P < 0{,}001$). Twenty patients (81%) died due to tumor progression, while two patients (9%) died of other causes (pulmonary embolism, diagnosis of second malignancy). Complete and partial remissions 6 months after finishing the treatment were achieved in four (20%) patients. In most cases, progression of the disease (60% of patients) was noted (Table II). No statistically significant differences were found in response to treatment in patients subgrouped by different parameters like age, gender, recurrent or residual tumor size, treatment method (HDRBT/PDRBT), primary treatment method. The application of hyperthermia also did not have a significant influence on the therapy results.

Serious late side-effects were seen in two (9%) patients. In both cases it was soft-tissue necrosis; in one

TABLE II.
Local control rates 4 weeks, 3 months and 6 months after finishing the treatment (assessed clinically and radiographically).

| | Local control rate | | |
|---|---|---|---|
| | after 4 weeks | after 3 months | after 6 months |
| Result | number/% | | |
| CR | 3/13 % | 2/9 % | 1/5% |
| PR | 9/41% | 6/28 % | 3/15% |
| NR | 5/23 % | 3/13 % | 0 % |
| progression | 5/23 % | 9/41 % | 12/60% |

CR = complete remission; NR = non?remission; PR = partial remission.

case further surgical treatment was necessary. No carotid blowouts or massive hemorrhage during implantation or thereafter were seen. There was no correlation between the occurrence of local complications and the applied radiation dose. Age, gender, treatment method (HDR/PDR), and primary treatment method had no influence on the development of complications as well.

## DISCUSSION

Recurrent cancer of the head and neck in the previously irradiated field poses a therapeutic challenge. Currently, the standard of care for such cases is surgical salvage. However, surgery is often not feasible and carries high risk of complications and morbidity. Similarly, reirradiation with EBRT is not recommended due to excessive morbidity. Chemotherapy is widely used as an alternative, but it generally gives poor response rate and in many cases is limited by its toxicity. Brachytherapy 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.[7,8]

Stomal recurrence of laryngeal cancer after total laryngectomy is a serious and in most cases fatal complication. It occurs in an overall incidence of 3% to 15 % and gives a median survival of 6 months.[1–3] Treatment is usually ineffective and limited to palliation controlling obstruction, hemorrhage, or infection. Various recommendations concerning management of stomal recurrence include symptomatic treatment, palliation with chemotherapy and radiation, and aggressive surgical salvage.[5–6]

The major problems of surgery for stomal recurrence are the inability to obtain clear margins due to the extent of the disease, and issues related to the reconstruction of the pharynx, esophagus, and stoma.[9] Gluckman et al.[10] present a multi-institutional experience analyzing surgical salvage for stomal recurrence. In the group of 41 patients who underwent definitive surgery, the overall 2-year survival was 16%. The results are comparable to those achieved in our group. Liu et al.[11] present even better results of 40.7% and 20.4% 1 - and 5-year survival rates, respectively, in a group of 23 patients with stomal recurrence treated surgically. Another Chinese group, Li et al.,[12] also investigates the issue of salvage treatment for stomal recurrence after total laryngectomy. Complete resection of tumor was performed in 33 out of 36 patients. Two patients died because of ruptures of major vessels 3 weeks and 2 months after the operation. The overall 1-year, 2-year, and 3-year survivals were 68.8%, 42.8%, and 12.5%, respectively.

EBRT, with or without chemotherapy, appears to be the treatment with the most potential for cure. Unfortunately, it is very often limited by its toxicity, especially in a previously irradiated area. Balm et al.[13] show eight patients with stomal recurrence after total laryngectomy who were treated with a combination of a cytotoxic regimen (vincristine sulfate, bleomycin, and methotrexate [VBM]) and EBRT. Five patients achieved complete local remission at 7 years, 3 years, 2 1/2 years, 14 months, and 8 months after treatment. Of the three patients who died, only one had recurrent disease around the tracheostoma. Two other patients were free of disease in the neck when they died 6 and 16 months after treatment, due to lung metastases and a second primary tumor in the lung, respectively. Sas-Korczyńska et al.[14] evaluate results of different treatment modalities in patients with inoperable recurrences of laryngeal cancer after total laryngectomy. In their group, 30 patients received EBRT alone and 12 patients received multidrug chemotherapy and EBRT. In 20 patients (47.6%), complete remission after therapy was observed but only nine (21.4%) patients survived without evidence of disease 2 years after EBRT. In patients treated with EBRT alone, 2 -year disease-free survival was observed in 16.7%; and in patients who received induction chemotherapy with Cisplatin, followed by radical irradiation, 2-year disease-free survival was observed in 40% of patients. Dawson et al.[15] consider conformal re-irradiation in the treatment of eight recurrent laryngeal cancers. The median survival following completion of the therapy was 11,8 months. In our subset of patients it was 9,5 months. The use of conformal techniques is, however, associated with the higher risk of severe late toxicity in comparison to interstitial HDR or PDR brachytherapy.

In worldwide literature, we have found only few reports dealing with the salvage treatment of stomal recurrent or residual disease with the use of brachytherapy. Three of them present intracavitary radiation by modification of tracheostomy tube. The method was described to be well tolerated and effective in relieving the symptoms related to the disease. Latham et al.[4] present the management of a 54-year-old man with multiple recurrences from a squamous cell carcinoma of the larynx. The dose given was 25 Gy at 5 mm over 25.2 h, and was achieved with minimal early or delayed side-effects. The patient had no further symptoms relating to the stomal recurrence until his death from metastatic disease 6 months later. Technical guidelines of using a special applicator combined with a tracheostomal tube are also presented by Schäfer et al.[16] and Janaki et al.[17] The method seems to be an interesting alternative in patients with stomal recurrence disqualified from

surgical salvage. It probably does not ensure covering the target volume, but it gives a good palliation and effectively relieves the symptoms. In the group analyzed by the authors, the treatment provided a good palliative effect in most patients. It improved the comfort of breathing, reduced fetor from the tracheostomy region, decreased cough, as well as reduced severity of local bleeding.

## CONCLUSION

The results of our study show that HDRBT and PDRBT are feasible in previously irradiated patients with recurrent or residual stomal tumor after total laryngectomy. They provide acceptable toxicity and good palliative effect.


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