

# Pulsed dose rate brachytherapy of lip cancer

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## Abstract

**Purpose:** To present our experience with pulsed dose rate brachytherapy (PDR BT) of lip cancer.

**Material and methods:** The study group included 32 T1-4N0M0 lip cancer patients with a median age of 71 years (ranged 41-87 years), treated with interstitial PDR BT to the planned total dose of 60-70 Gy; 1 Gy/pulse, pulses repeated every hour a day. There were 26 untreated patients, and six patients after previous surgery including five implanted at the time of cancer relapse.

**Results:** PDR BT was delivered over few days and was well tolerated. After therapy, all patients experienced temporary, usually mild, acute mucositis. Late severe (Grade 3) mucositis of oral vestibule mucosa occurred in one case. Among 31 patients who completed the therapy, local control was achieved in 29 (93.5%). One patient with recurrent upper lip T2 tumor was successfully salvaged surgically, another one died due to persisted T3 lip tumor with lymph node metastases. Overall, four patients developed neck nodal cancer relapse and two – distant metastases. The 5-year local control, and all-cause overall survival probabilities are 94% and 73%, respectively. Good/excellent cosmetic and functional outcome was obtained in all but two patients.

**Conclusions:** PDR at the dose of 1 Gy/pulse is effective and well tolerated BT technique in treating lip cancer patients.

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**Key words:** brachytherapy, lip cancer, pulsed dose rate.

## Purpose

Carcinomas of the lip are relatively rare tumors that can successfully be treated with different methods. Surgery continues to be the best option for early tumors if lip function can be preserved. External beam radiotherapy has been applied for large tumors, as well as for older patients. Brachytherapy (BT) as an exclusive definitive treatment, yields excellent results for local control with very satisfying cosmetic results in small and intermediate tumors. BT may be also used as an adjunct to surgery in cases with positive/close margin. Several authors published their experience with low dose rate (LDR), and high dose rate (HDR) BT in treating lip carcinomas.

Pulsed dose rate (PDR) treatment is a new BT modality combining the physical advantages of HDR technology (isodose optimization, radiation safety) with radiobiological advantages of conventional continuous LDR BT. To achieve the equivalent of LDR effect while using PDR treatment strategy, similar average dose rate should be considered [1,2]. PDR technique was demonstrated as effective, as well as safe treatment method with excellent functional and cosmetic results in many head and neck tumors. Despite its favourable features, PDR BT has rarely been used in lip carcinomas. Our early experience with PDR BT employed in lip cancer patients was pre-

sented elsewhere [3]. Here we present larger series with longer follow-up.

## Material and methods

The study group consisted of 32 consecutive T1-4N0M0 lip cancer patients who underwent interstitial PDR BT procedure at the Medical University of Gdańsk, Poland between July 1999 and September 2011 (Table 1). Computed tomography scans or magnetic resonance imaging were not performed in work-up staging before PDR treatment. There were 21 patients (66%) above 65 years of age, 17 (53%) above 70 years, and 5 (19%) above 80 years. All tumours were located in the lower lip, except one patient with upper lip disease. Six patients (19%) were previously excluded from surgery due to severe comorbid conditions. A histology of squamous cell carcinoma was diagnosed, except for one woman with basaloid carcinoma. Six patients (19%) underwent prior surgery. One of the patients (with positive margin) was implanted as an adjuvant treatment, and the remaining five at the time of local cancer recurrence. The remaining 26 patients were administered exclusive BT. The planned total dose of BT was 60-70 Gy. The dose per pulse (pd) repeated every hour a day was 1.0 Gy in all but one patient, who was treated with 2.5 Gy pd (this decision was made individually in relation to clinical condition of

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elderly patient with dementia as well as cardiovascular system disorders associated with general atherosclerosis). Flexible tubes to the primary tumor/tumor excision site were placed using local anaesthesia. Sedation was added if required. Implantations were carried out according to the Paris system. Needles were placed equidistantly, parallel to the skin's surface, forming triangles. The standardized templates for a triangular array were not used. Mould therapy was not used, also a spacer (such as a mould or a similar treatment device) to reduce doses to the normal tissues such as mandible, and apposite lip was not inserted at the time of the therapy. After tube placement to reduce the oedema around the implant some patients received steroids (8 mg dexamethasone intravenously). Prophylaxis with antibiotics was not routinely used. After tube implantation, radiographic verifications of tube placement were taken, digitized, and entered into a BT planning system (PLATO, version 14.1<sup>®</sup>, Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). The planned target volume was defined as the volume encompassing the tumour/tumor excision site with approximately 5-10 mm safety margin around the gross tumor volume whenever possible, as detected by clinical findings and additional histological data, specified by the physician participating in tube placement. When applicable, the skin dose was reduced by keeping a distance of at least 5-10 mm from the first dwell position of the stepping source. The dosimetry was calculated using geometrical optimization on volume, with manual modifications in some cases. Thus, the prescribed dose was defined, beside typical value of 85% of mean central dose (MCD) also as 90% of MCD. In one case due to unsatisfactory dose distribution of the implant, the needles were removed and the procedure was repeated after 3 days. PDR BT was delivered with the use of Microselectron PDR<sup>®</sup> unit (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). Neither prophylactic external beam radiotherapy to the neck nodal region nor prophylactic lymphadenectomy were performed. After treatment completion, all patients were followed-up regularly. Follow up ranged between 14 and 164 months.

Local tumor control, regional/distant control, and overall survival were estimated using the Kaplan-Meier analysis.

## Results

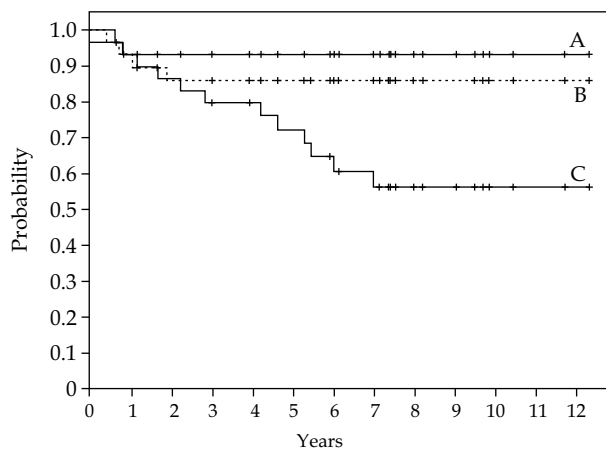
The median number of plastic tubes used per lip implant was 3 (ranged 2-9) (Table 1). For the entire group of patients, the average volume for the prescribed dose ( $V_{100\%}$ ) was 8.3 cm<sup>3</sup> (ranged 1.3-29.3 cm<sup>3</sup>). All but one patient completed BT. One case of 87-years old T<sub>3</sub> lip cancer patient administered BT at 2.5 Gy pd deteriorated neurologically, and died after receiving 42.5 Gy. Apart from the above patient, all other PDR BT applications lasting almost three days were tolerated well. During the therapy, eating was not restricted and the patients were drinking through a straw. Due to lip pain, some patients required nonopioid analgetics. No significant bleeding associated with catheters removal was observed. At the treatment completion, all patients experienced acute, temporary, and moderate (RTOG Grade 1-2) mucositis and skin infection for one to three weeks, requiring antibiotics administration in 9 cases (29% subjects). Late severe

**Table 1.** Patient and treatment characteristics (n = 32)

Variable	n (%)
Age (years)	
Range	41-87
Median	71
UICC TNM stage at the time of brachytherapy (n = 31)	
T1N0M0	9 (29)
T2N0M0	18 (58)
T3N0M0	3 (10)
T4N0M0	1 (3)
Squamous cell differentiation (n = 31)	
G1	19 (61)
G2	3 (10)
G3	1 (3)
Not assessed	8 (26)
The dose of brachytherapy (n = 31) (Gy)	
60	4 (13)
66	8 (26)
70	19 (61)
Number of tubes	
2	1 (3)
3	26 (81)
5	3 (9)
8	1 (3)
9	1 (3)
Volume at the prescribed isodose ( $V_{100}$ ) (cm <sup>3</sup> )	
Range	1.3-29.3
Median	5.8

(RTOG Grade 3) toxicity of oral vestibule mucosa occurred in one patient (3%) at 12 months after therapy. This side effect resolved in 3 months with local treatment. The extraction of the teeth irritating the mucosa supported healing process. No other serious late toxicity was noted. All patients presented some atrophy of the irradiated tissue including two cases presented with late Grade 2 skin reaction. These skin changes progressed over time necessitating local treatment.

There were two local treatment failures (6%), including a case of persistent T3 local disease after receiving 70 Gy, who developed neck lymph node metastases and died 33 months after BT. The second local treatment failure occurred in a man with T2 upper lip cancer at 8 months after BT. The second patient was successfully salvaged with surgery including elective neck lymphadenectomy, and remained free of disease for the subsequent 4 years. Thereafter, he was diagnosed with buccal carcinoma, probably of primary origin. Overall, regional nodal cancer metastases at 8, 11, 12, and 18 months after therapy occurred in four patients, two of them presented with T2 stage, and the remaining two with T1 and T3 stage. Among these patients,



**Fig. 1.** Kaplan-Meier estimation of local control (A), local/regional control (B) and overall survival (C) irrespective of cause of death ( $n = 31$ )

one woman is alive for subsequent 8 years after dissection of involved lymph nodes, and receiving external beam radiotherapy to the neck region. Another one, a 54-year old male with tumor T2 G1 died due to uncontrolled cancer dissemination to the bones 38 months after BT. Bones and lungs lesions were also observed in another 71-old patient with T2 G1 tumor who died 7 months after BT completion. There were three patients diagnosed with buccal, laryngeal, and renal cancer following lip carcinoma. At the last follow up on September 2012, death resulting from intercurrent disease occurred in 8 patients, and four patients died due to lip cancer. For the group of 31 assessable patients, the actuarial local control at 5 years was 94% (100% for T1 tumors), and 5-year all-cause overall survival was 73% (Fig. 1).

Good or excellent functional/cosmetic results were obtained in 28 (90%) out of 31 assessable patients. The only unfavourable cosmesis was observed in a patient salvaged surgically for recurrence, which required wide excision. This patient will have reconstructive surgery because of microstomy. Saliva leakage due to irregular surface of the lip was noted in another patient.

## Discussion

Interstitial BT with the use of both LDR and HDR for lip carcinomas has been applied with excellent local control, survival and good cosmetic outcome. Considerable experience has accumulated with the former technique [4-13]. In the largest series of 237 T1-T4 lip cancer patients treated with LDR  $^{192}\text{Ir}$  (65-68 Gy), a 95% local control rate at 5 years was reported [5]. Local control rate of 90-98% was reported by others [6,11,13]. Three-year local control of 88% and cause specific survival of 91% in a group of 39 T1,2, and T4 lip cancer patients (mean age 73 years) treated with HDR BT (total dose 40.5-45 Gy in 8-10 fractions b.i.d) was reported [10]. In the comparative study of LDR and HDR in a group of 100 patients (median age of 67 years), similar rate of severe mucosal toxicity between groups was shown [4]. The most recent study from Ontario demonstrated the usefulness of LDR BT with permanent gold grain implants [14].

In this series of patients, we evaluated the efficacy of PDR BT in lip carcinomas. Similarly to other series, elderly patients constitute substantial number of our population. It is noticeable that this series includes some early stage lip cancer patients non-amenable to primary surgery, because of contraindication to general anaesthesia, therefore were implanted under local anaesthesia. The actuarial local control at 5 years in our series was 94%. In the recently published Swedish experience of 43 T1-3N0 lip cancer patients (T1 in 51%) treated with PDR BT, 5-year actuarial local control rate of 94.5% and disease-free survival of 86.4% were reported [15]. 31% of these patients were treated after non radical surgery. The authors used a minimum target dose of 60 Gy in 12 pulses per day (intervals 2 hours; 0.83 Gy pd), except for patients after non radical surgery ( $n = 6$ ), and T2-3 large volume tumors ( $n = 3$ ) who were administered a dose of 55 Gy and > 60 Gy, respectively. The prescribed dose was defined as 85% of MCD in the central plane according to the Paris system. The mean treated volume in this series was 14.9 cm<sup>3</sup>, and a median of 4 catheters was used.

All our patients experienced a transitory acute mucositis with secondary late radiodermatitis in some cases. Despite routine use of antibiotics, during the implant and plastic plate between the teeth and the lip during the pulses at day-time an intensive mucositis in the treatment volume in all patients were also reported by others [15]. These reactions were scored most as Grade 1 SOMA/LENT skin toxicity (with no teleangiectasias).

To reduce the risk of secondary infections prophylactic, antibiotics in head and neck cancer patients treated with interstitial BT were recommended by the American Brachytherapy Society [16]. Severe (Grade 3) acute mucositis toxicities were experienced by two of four stage I lip cancer patients managed with PDR BT at a median dose of 41.1 Gy (0.4-0.5 Gy pd) (with the use of flexible tubes) in the series by de Pree *et al.* [17].

The only one late severe side effect accompanying PDR BT in our series includes soft tissue ulceration of oral vestibule mucosa, which was successfully healed. Transient soft tissue necrosis in one patient was observed by Johansson *et al.* [15].

Good cosmetic treatment result is of primary importance in the face. In our series, worse cosmesis and function was observed in a man salvaged surgically due to local cancer relapse. In all but one patient, good/excellent functional and cosmetic outcome were obtained, including cases with large tumors. In Swedish series, saliva leakage was seen in 14% of patients administered PDR BT [15].

Concerning the implantation technique, it is possible to use both rigid and plastic tubes with or without plastic templates to get a fixed distance between them. We have chosen flexible tubes as they gave superiority in terms of patient's convenience during therapy. We also used no templates. Despite no fixed distance between tubes, the stepping source technology with the associated optimisation algorithm allows to achieve sufficient dose homogeneity. Due to unsatisfactory dose distribution, implantation had to be repeated in only one case. To achieve local control by PDR BT alone, the doses have to be applied within the dose range well known for LDR BT, ie. 60-70 Gy. The recommended

by GEC-ESTRO optimal dose rate with PDR technique is from 0.3 to 0.7 Gy/hour for head and neck squamous cell carcinomas [18]. However, the optimal time-dose pattern for PDR continues to be debated. A dose of 1 Gy per pulse (i.e. the upper limit of dose rate for keeping hypothetical favourable biological features of PDR) performed in all but one patient in our series was chosen for organizational reasons – to shorten treatment time. This resulted in slightly higher biological doses as compared to continuous LDR. Moreover, this might have increased the risk of toxicity [19]. The dose rate above 0.57 Gy/hour, the total dose above 71 Gy as well as a high number of wires (> 5) were reported to be the major risk factors for complications in patient with the oral cavity carcinomas administered continuous LDR BT [20].

### Conclusions

PDR BT at the dose of 1 Gy/pulse is a safe and convenient method in lip cancer treatment including elderly patients. It provides excellent local control rate with limited toxicity. To reduce secondary infections after the therapy, prophylactic antibiotics should be considered in all cases.

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