# High dose rate versus low dose rate brachytherapy in the treatment of tongue carcinoma – a radiobiological study

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Low dose rate (LDR) brachytherapy is a well established treatment for the early stages of tongue cancer. High dose rate (HDR) afterloading devices have replaced LDR brachytherapy in many radiotherapy departments, but the effect and safety of HDR brachytherapy in comparison with LDR brachytherapy for interstitial applications is an unresolved question. The aim of our radiobiological study was to utilize dose volume histograms from patients treated in our institution to simulate the risk of complication of LDR and HDR brachytherapy. Normal tissue complication probabilities (NTCP) of acute mucositis, late mucosal necrosis and osteoradionecrosis of two HDR brachytherapy schedules (18 x 3 Gy bid and 10 x 6 Gy bid) and of LDR brachytherapy with identical tumor control probability were compared using data from 8 brachytherapy applications. A linear quadratic (LQ) model was used to calculate the biologically equivalent doses, the effective volume method of Kutcher and Burman and Lyman's model was used to calculate NTCP. The Student's two-tailed test was used for statistical analysis. For 18 x 3 Gy bid the risk of acute mucositis and of late mucosal necrosis was 1.48 and 1.66 times higher with HDR in comparison with LDR brachytherapy. For 10 x 6 Gy bid the risk of acute mucositis, mucosal necrosis and osteoradionecrosis was 1.3, 3.44 and 13.18 times higher with HDR brachytherapy. All differences were statistically highly significant. Our radiobiological study supported the hypothesis that HDR has a higher risk of complication in comparison with LDR brachytherapy for the same tumor control probability.

*Key words*: *tongue cancer, brachytherapy, low dose rate, high dose rate*

Brachytherapy (BT) is a well established treatment for the early stages of tongue cancer. BT is as effective as surgery for tumor control with better functional and cosmetic results in the majority of cases. In comparison with external beam radiotherapy brachytherapy allows the delivery of higher doses of radiation over a shorter period of time with reduced volume of irradiated healthy tissues. The tumor control is improved and postradiation xerostomia and soft tissue fibrosis are less frequent.

Most of experiences with BT to treat tongue cancer was achieved with the manual afterloading technique and iridium wires with continuous low dose rate (LDR) irradiation. Continuous LDR BT favors normal tissue repair during irradiation and results in a beneficial therapeutic ratio between tumor control probability and normal tissue complication probability. High dose rate (HDR) afterloading devices have replaced LDR brachytherapy in many radiotherapy departments. HDR BT is biologically more effective in comparison with LDR BT, which is more profound for the normal late reacting tissues than for the tumor. The consequence is a less beneficial therapeutic ratio. HDR brachytherapy must be fractionated and numerous small fractions are recommended to allow the repair of healthy tissues and to achieve biological equivalence with LDR brachytherapy.

As regards the use of HDR BT in tongue cancer there are only controversial results of limited values available to date [1]. HDR is often considered to be dangerous for interstitial implants due to the higher risk of complications. In our institution we started HDR BT to treat oral cancer in 2001 and our preliminary clinical findings were published [2]. Since 2005 we have used CT-based planning of brachytherapy implants. The aim of our radiobiological study was to use the geometry of performed brachytherapy applications and dose volume histograms for radiobiological modelling of the complication risk of HDR and LDR BT in the treatment of tongue cancer.

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**Figure 1. The technique of brachytherapy**



**Figure 2. Delineation of clinical target volume, mucosa in risk and mandibula ( red – target volume, yelow – mucosa in risk, blue – mandibula)**

## Patients and methods

*The brachytherapy technique.* HDR BT without external beam radiotherapy is used for patients with T1-2N0M0 tongue carcinoma after excisional biopsy in our institution. The technique of brachytherapy is based on the use of plastic tubes applied in double planes 1 cm apart. The distribution of catheters in the central plane is either in equilateral triangles or in squares. The catheters are secured by plastic buttons located on the surface of the tongue and the submandibular region. The catheters protrude 10 mm above the tongue to ensure a sufficient dose is applied to the tongue surface (Fig. 1). The prescription points are set at 5 mm away from the catheters. Dose distribution is calculated using the Abacus – GammaMed planning system; as of 2005 the calculation is based on CT planning and Brachyvision planning system (Varian, USA). For irradiation delivery we use HDR device (Gammamed, MDS Nordion, Hahn, Germany). The prescribed dose is 54 Gy in 18 fractions, 3 Gy twice daily with an interval of at least 6 hours between fractions and with a gap during weekends. For our radiobio-

logical study we have used data from 8 patients planned using the Brachyvision planning system. The details of brachytherapy are presented in Table 1.

*Method of HDR and LDR implants comparison.* We compared the risk of complications of our HDR regime 18 x 3 Gy twice daily/ 11 days and of HDR regime 10 x 6 Gy twice daily/6 days frequently used in the literature [3, 4, 5] with LDR doses biologically equivalent for the tumor. To calculate the biologically equivalent doses we used the formula BED (Biologically Effective Dose) = Nd [1+d/($\alpha$/$\beta$)] for fractionated HDR BT, where N = number of fractions, d = dose per fraction. For continuous LDR brachytherapy BED = D [1+2R/$\mu$($\alpha$/$\beta$)], where D = R.T, R = 0.5 Gy/hr, T = total time of continuous irradiation, $\mu$ = 0.5 Gy$^{-1}$/hr. We the assumed ratio $\alpha$/$\beta$ = 10 Gy for tumor and early reacting tissues and $\alpha$/$\beta$ = 3 Gy for late reacting tissues [6] .

We have chosen acute mucositis, late mucosal necrosis and late osteonecrosis of the mandible as the most relevant complications of brachytherapy of the tongue.

Planning CT scans were performed with a separation of 3 mm between slices. We delineated the contours of the clini-

**Table 1. Characteristics of brachytherapy implants**

| Patient No | No of catheters | Minimum target dose (MTD) | Volume of MTD (cm³) | Mean central dose (Gy) | V 150 | Dose homogeneity index |
|---|---|---|---|---|---|---|
| 1 | 8 | 18 x 3 | 15.4 | 4.3 | 5.8 | 0.71 |
| 2 | 5 | 18 x 3 | 14.4 | 3.8 | 6.0 | 0.79 |
| 3 | 11 | 18 x 3 | 20.6 | 3.4 | 4.8 | 0.88 |
| 4 | 10 | 18 x 3 | 19.8 | 5.6 | 11.9 | 0.54 |
| 5 | 9 | 18 x 3 | 18.7 | 5.2 | 8.2 | 0.58 |
| 6 | 8 | 18 x 3 | 13.6 | 5.8 | 7.7 | 0.52 |
| 7 | 7 | 18 x 3 | 14.0 | 3.8 | 5.0 | 0.79 |
| 8 | 8 | 18 x 3 | 13.6 | 4.6 | 7.2 | 0.65 |

V 150 = volume encompassed by the isodose corresponding to 150% of the mean central dose

cal target volume (CTV – tumor with 1 cm margin), mucosa in risk (CTV with 2 cm margin) and mandible (Fig. 2). Differential and cumulative dose volume histiograms (DVH) (Fig. 3) were obtained and used to calculate BED, LQED2 (biologically equivalent dose for fractionated radiotherapy 2 Gy/day, 5 fractions/week), tumor control probability (TCP) and normal tissue complication probability (NTCP) for each patient. The effective volume method of Kutcher and Burman was used to reduce non – uniform tissue irradiation to a uniformly irradiated dose equivalent, where a fraction of the organ, $V_{eff}$, receives the maximum organ dose [7]. NTCP was calculated using Lyman's model [8] and tolerance parameters according to Emami et al. [9] were applied (Table 2). The risk of acute mucositis was assessed according to Fowler's model based on analysis of clinical data about acute mucosal reactions from clinical trials with altered fracionation [10]. For TCP calculation we used a model based on Poisson statistics incorporating the parameters of a linear quadratic model [11]. Calculation was performed with the program BioGray [12]. The output of the simultaneous display of these radiobiological parameters for one patient is shown in Fig. 4. The statistical significance of the differences between HDR and LDR was assessed using a two-tailed Student's test.
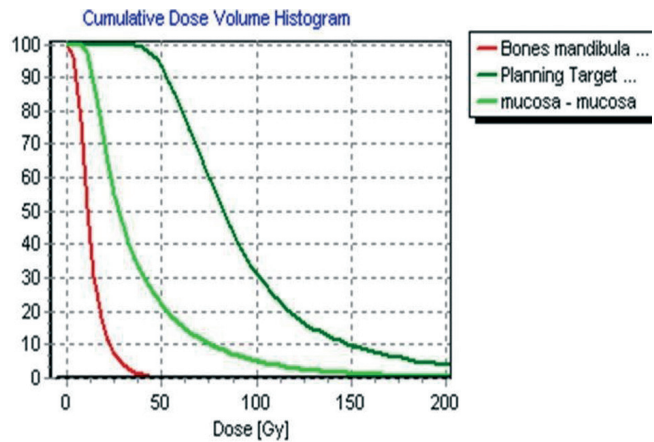
## Results

For HDR scheme 18 x 3 Gy bid/11 days BED = 70.2 $Gy_{10}$ (LQED$_2$ = 58.5 Gy) and the corresponding LDR dose the



**Figure 3. Cummulative dose volume histiograms**

**Table 2. Fitted parameters by Kutcher Burman for Lyman's model of NTCP**

|  | m | n | NTD$_2$ 5/5 | NTD$_2$ 50/5 | NTD$_2$ 25% early effects |
|---|---|---|---|---|---|
| Acute mucositis | 0.15 | 0.1 |  |  | 66 Gy |
| Late mucosal necrosis | 0.18 | 0.1 | 56 Gy | 68 Gy |  |
| Osteoradionecrosis | 0.07 | 0.1 | 60 Gy | 75 Gy |  |

NTD$_2$ 5/5 and NTD$_2$ 50/5 represent normalized total doses (in Gy) in conventional fractionation 2 Gy/day which results in 5 % and 50 % of complications /5 years to whole organ, respectively. The acute mucositis was calculated by Fowler's model (14) with accepted tolerance NTCP$_{acute}$ = 25 %
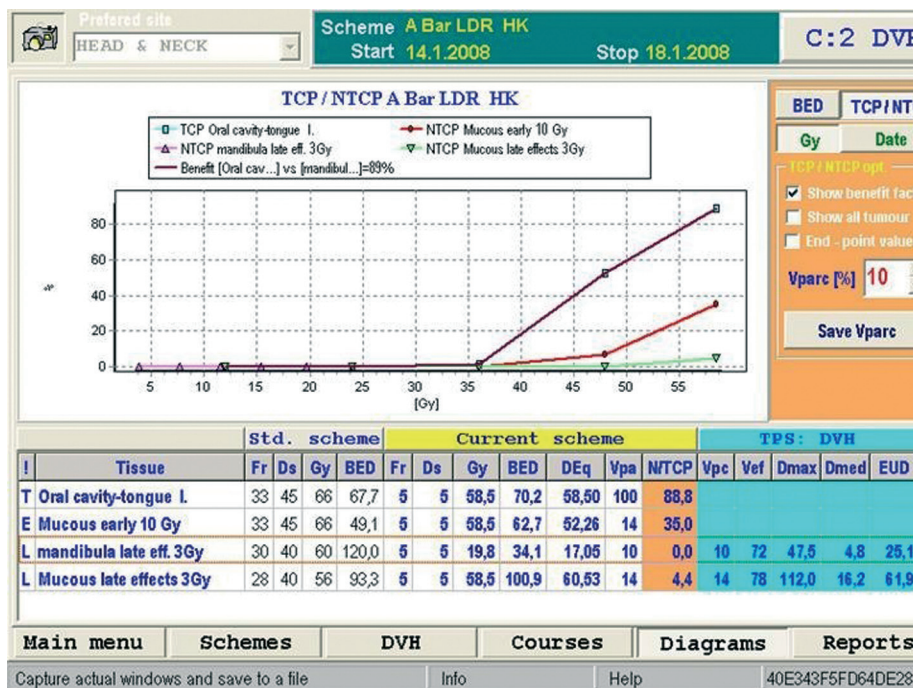


**Figure 4. The output of BioGray**

**Table 3. HDR 54 Gy/18 F/3 Gy (bid)/11 days vs. equivalent LDR 58.5 Gy/117 hours**

| Patient No | NCTP (%) Acute mucositis | | NCTP (%) Late mucosal necrosis | | NCTP (%) Osteonecrosis | |
|---|---|---|---|---|---|---|
| | HDR | LDR | HDR | LDR | HDR | LDR |
| 1 | 51.4 | 36.7 | 5.7 | 4.1 | 0 | 0 |
| 2 | 50.1 | 32.8 | 3.8 | 2.4 | 0 | 0 |
| 3 | 51.4 | 35.0 | 5.7 | 3.4 | 0 | 0 |
| 4 | 52.7 | 35.5 | 8.3 | 5.1 | 0 | 0 |
| 5 | 49.6 | 32.4 | 3.4 | 2.1 | 0 | 0 |
| 6 | 51.0 | 33.6 | 4.9 | 2.9 | 0 | 0 |
| 7 | 51.0 | 34 | 2.4 | 0.6 | 0 | 0 |
| 8 | 52.7 | 36 | 3.4 | 2.1 | 0 | 0 |

**Table 4. HDR 60 Gy/10 F/6 Gy(bid)/6 days vs. equivalent LDR 80 Gy/160 hours with a dose rate 0.5 Gy/hour:**

| Patient No | NCTP (%) Acute mucositis | | NCTP (%) Late mucosal necrosis | | NCTP (%) Osteonecrosis | |
|---|---|---|---|---|---|---|
| | HDR | LDR | HDR | LDR | HDR | LDR |
| 1 | 100 | 96.7 | 70.2 | 18.5 | 9,8 | 0,8 |
| 2 | 100 | 96.9 | 78.2 | 24.2 | 12,5 | 0,9 |
| 3 | 100 | 98.7 | 86.9 | 32.4 | 14,8 | 2,0 |
| 4 | 100 | 96.9 | 82.9 | 24.2 | 23,7 | 0,8 |
| 5 | 100 | 96.7 | 74.9 | 21.7 | 14,8 | 0,8 |
| 6 | 100 | 96.7 | 63.5 | 15.1 | 15,8 | 2,2 |
| 7 | 100 | 96.3 | 63.5 | 15.1 | 9,8 | 0,4 |
| 8 | 100 | 96.7 | 74.9 | 21.7 | 14,8 | 0,8 |

biologically equivalent for tumor is 58.5 Gy/115.4 hr (dose rate R = 0.5 Gy/hr). TCP is 88.8% and 74.5% for T1N0M0 and T2N0M0 respectively. Table 3 shows the NTCP values for individual applications. NTCP of HDR BT 18 x 3 Gy bid/11 days was 51.2 ± 1.1%, 4.7 ± 1.9% and 0% for acute mucositis, late mucosal necrosis and osteoradionecrosis respectively. For LDR it was 34.5 ± 1.5%, 2.84 ± 1.4 % and 0%. The risk of acute mucositis was 1.48 times higher and the risk of late mucosal necrosis was 1.66 times higher for HDR in comparison with LDR. This difference was statistically significant (p = 0.011 and p = 0.0001 for acute mucositis and late mucosal necrosis, respectively).

For HDR scheme 10 x 6 Gy bid/6 days BED = 96 $Gy_{10}$ ($LQED_2$ = 65 Gy) and the corresponding LDR the dose is 80 Gy/160 hr (dose rate R = 0.5 Gy/hour). TCP is 99.6% and 98.7% for T1N0M0 and T2N0M0 respectively. The NTCP values for individual patients are shown in table 4. NTCP of HDR BT 10 x 6 Gy bid/6 days was 100%, 74.4 ± 8.4% and 14.5 ± 4.4% for acute mucositis, late mucosal necrosis and osteoradionecrosis respectively. For the equivalent LDR it was 96.9 ± 0.7%, 21.6 ± 5.6% and 1.1 ± 0.6%. The risk of acute mucositis was 1.3 times higher, the risk of late mucosal necrosis was 3.44 times higher and the risk of osteonecrosis was 13.18 times higher for HDR in comparison with LDR. These differences were statistically significant (p < 0.0001 for both acute and late reactions).

## Discussion

Iridium[192] interstitial BT with a low dose rate has been reported as a successful treatment modality for oral cancer in a number of studies. The miniaturization of high activity of radioisotopes along with sophisticated computer technology has led to the establishment of remote afterloading HDR BT. The advantages of HDR compared with LDR are: greater ability to conform the implant dosimetry to the target volume, decreased risk of radiation exposure for medical staff, and better dose distribution homogeneity within the target volume with a potential for less normal tissue irradiation. In addition, because of the decreased radiation delivery time, there is less likelihood of organ movement and a higher likelihood of the patient being treated as an outpatient. However, because of the differences in the radiation biological effect of high dose per fraction, there are some concerns remaining regarding the risk of increased late complications.

The dose prescription for HDR BT is based upon extrapolation of LDR experience by mathematical modeling. The linear quadratic model is used to calculate the equivalent biological dose for the tumor to achieve tumor control comparable with the results of well established LDR schedules, but HDR doses and fractionation vary between different centres. The clinical information available to evaluate tumor control and the side effects of HDR BT for tongue carcinoma in comparison with LDR brachytherapy is insufficient and the questions

about the safety of interstitial HDR brachytherapy remain open.

Umeda et al. [13] compared the results in 25 patients with stage I-II tongue cancer treated by HDR BT with a group of patients treated with traditional LDR brachytherapy. An average dose of 59 Gy (6 Gy x 9-10 fractions/5days) was administered. Nine (36%) of the 25 patients in the HDR group showed local recurrence. Mandibular bone necrosis was found in 5 patients. The local control and the incidence of osteonecrosis were significantly higher in the HDR group than in the LDR group.

Lau et al. [14] reported only 53% local control rate and a trend towards a higher incidence of severe complications for the HDR patients compared to historical controls. They treated these patients with a total dose of 45.5 Gy/7 fractions.

Inoue et al. [4] reported on Phase III trial comparing 25 eligible patients treated with LDR BT and 25 patients treated with HDR BT for early mobile tongue cancer. Hyperfractionated HDR BT with a total dose of 60 Gy/10 fractions/1 week was used. The five-year local control rates for LDR and HDR groups were 84% and 87% respectively. A tongue ulcer occurred in 1 patient for both groups. Bone exposure occurred in 2 patients in the HDR group. For 1 of the 2 patients with bone exposure the spacer, which reduces the dose to mandible, was not used.

Kakimoto et al. [15] compared the results from 61 patients treated with LDR BT and 14 patients treated with HDR BT 32-60 Gy/8–10 fractions/5–7 days. The tumor control was almost similar, with no significant differences in the incidence of soft tissue ulcer and bone exposure (25 out of 61 and 3 out of 14 patients in the LDR and HDR group respectively).

Yamazaki et al. [5] examined the comparability of LDR BT with HDR BT in patients with early oral tongue cancer. HDR BT was used for 58 patients to a total dose of 48–60 Gy in 8-10 fractions. The 5-year local control was 84%, which was comparable with the LDR group. Complications after HDR BT were 10% and similar to that after LDR BT of 6%.

From the published clinical results it is hardly possible to draw conclusions about the efficacy and safety of HDR BT in tongue cancer. In our institution we use HDR BT for the early stages of tongue cancer since 2001 with hyperfractionation 18 x 3 Gy bid [2]. Doses per fraction ≤ 3 Gy are recommended in the literature [1]. Our schedule was assumed to be biologically equivalent to 65 Gy according LQ model ($\alpha/\beta$ for TU = 10 Gy, $\alpha/\beta$ for late tissue = 3 Gy, repair $\mu$ for TU = 1.2 h$^{-1}$, $\mu$ for late tissues = 0.46, repopulation k for TU = 0.3 Gy/day, k for late tissues = 0.01 Gy/day). Recently a new value of the repair constant $\mu$ = 0.5 Gy was recommended [6]. With this new value our fraction is equivalent to 58.5 Gy LDR.

Inhomogeneity of irradiation and a steep dose gradient are essential features of brachytherapy. LQ model allows us to calculate biologically effective doses at certain points with no volumic factor; however more sophisticated radiobiological models are more preferable for evaluating tumor control and the probability of normal tissue complications, moreover the quality parameters of the implant play an important role. Attempting to contribute to a deeper understanding of the ability of HDR BT to replace LDR BT for tongue carcinoma we used the geometry of implantation of 8 patients with CT-based planning of brachytherapy while respecting the irradiated volume calculated from DVH available as a "sub-product" from 3D-treatment planning system (3D-TPS) and consequently, to perform a radiobiological simulation and modelling of TCP and NTCP for both HDR and LDR BT. In modern methods of external beam radiotherapy as three-dimensional and dose-intensity-modulated techniques it is often difficult to choose between competing dose volume histograms when they cross one another. NTCP model is a suitable means of evaluating the biological consequences of inhomogenous normal tissue irradiation presented by physical dose volume histiograms. It is increasingly used for radiobiological considerations in external beam radiotherapy and seems to be suitable for comparing the risk of complications of HDR vs. LDR BT.

Our results show that HDR BT has a higher risk of complications in comparison with LDR BT with the same TCP and that this risk is more pronounced for late than acute reactions. The doses of 6 Gy per fraction had a worse therapeutic ratio than the doses of 3 Gy per fraction. The probability of complications with 10 x 6 Gy bid was extremely high, which was in contrast with the clinical results of the Inoue study, where severe late effects were observed in only 3 out of 25 patients. The explanation is that in this study all patients were treated with a single-plane implantation and the treated volume was 10–15 cm$^3$. In our study all patients were treated with double-plane implants and the average volume of application was 16.3 cm$^3$.

The HDR BT in cervical carcinoma provide equivalent TCP and NTCP as LDR BT. In this situation the organs at risk, rectum and urinary bladder, are more distant from the target volume and because of the steep gradient of the brachytherapy dose, even steeper for BED of late tissues than for physical dose, these organs can be spared by HDR BT [16]. In BT of tongue cancer the mucosa at risk and mandible are in the close vicinity of the target volume and are at a higher risk of complications with HDR BT in comparison with LDR BR.

In conclusion, the results of our radiobiological study support the hypothesis that HDR BT of tongue cancer may imply a higher risk of normal tissue complication than LDR BT.

## References

[1]    Strnad V. Treatment of oral cavity and oropharyngeal cancer. Indications, technical aspects, and results of interstitial brachytherapy. Strahlenther Onkol 2004; 180: 710–717.

[2]    Petera J, Doležel M, Jirousek Z et al. High dose rate brachytherapy in the treatment of oral cancer – the preliminary one institution experience. Neoplasma 2006; 53: 232–236.

[3]    Leung TW, Wong VY, Wong CM et al. High dose rate brachytherapy for carcinoma of the oral tongue. Int J Ra-

diat Oncol Biol Phys 1997; 39: 1113–1120. doi:10.1016/S0360-3016(97)00376-3

[4] Inoue T, Inoue T, Yoshida K et al. Phase III trial of high- vs. low-dose-rate interstitial radiotherapy for early mobile tongue cancer. Int J Radiat Oncol Biol Phys 2001; 51: 171–175. doi:10.1016/S0360-3016(01)01561-9

[5] Yamazaki H, Inoue T, Yoshida K et al. Brachytherapy for early oral tongue cancer: low dose rate to high dose rate. J Radiat Res 2003; 44: 37–40. doi:10.1269/jrr.44.37 PMid:12841597

[6] Dale R, Jones B, editors. Radiobiological modelling in radiation oncology: London: The British Institute of Radiology, 2007.

[7] Kutcher GJ, Burman C, Brewster L et al. Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. Int J Radiat Oncol Biol Phys 1991; 21: 137–146.

[8] Lyman JT, Wolbarst AB. Optimization of radiation therapy, III: A method of assessing complication probabilities from dose-volume histograms. Int J Radiat Oncol Biol Phys 1987; 13: 103–109.

[9] Emami B, Lyman J, Brown A et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21: 109–122.

[10] Fowler JF, Harari PM, Leborgne F et al. Acute radiation reactions in oral and pharyngeal mucosa: tolerable levels in altered fractionation schedules. Radiother Oncol 2003; 69: 161–168. doi:10.1016/S0167-8140(03)00231-7 PMid:14643953

[11] Warkentin B, Stavrev P, Stavreva N et al. A TCP-NTCP estimation module using DVHs and known radiobiological models and parameter sets. J Appl Clin Med Phys 2004; 5: 50–63. doi:10.1120/jacmp.26.149 PMid:15753933

[12] Matula P, Končík J, Jutka K et al. Modelling of dose-volume tolerance of normal tissues. Acta Chemotherapeutica 2008; 17: 80–95.

[13] Umeda M, Komatsubara H, Nishimatsu N et al. High-dose rate interstitial brachytherapy for stage I-II tongue cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000; 90: 667–670. doi:10.1067/moe.2000.110087

[14] Lau HY, Hay JH, Flores AD et al. Seven fractions of twice daily high dose-rate brachytherapy for node-negative carcinoma of the mobile tongue results in loss of therapeutic ratio. Radiother Oncol 1996; 39: 15–18. doi:10.1016/0167-8140(95)01686-4 PMid:8735489

[15] Kakimoto N, Inoue T, Inoue T et al. Results of low- and high-dose-rate interstitial brachytherapy for T3 mobile tongue cancer. Radiother Oncol 2003; 68: 123–128. doi:10.1016/S0167-8140(03)00055-0 PMid:12972306

[16] Deehan C, O'Donoghue JA. Biological equivalence of LDR and HDR Brachytherapy. In: Mould RF, Battermann JJ, Martinez AA, Speiser BL, editors. Brachytherapy from radium to optimization. The Netherlans: Nucletron International, 1994: 19–33.