High dose rate brachytherapy in the treatment of oral cancer – the preliminary one institution experience*

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Low dose rate brachytherapy is well established treatment modality of oral cancer. Data about high dose rate brachytherapy (HDR BT) are still scarce with heterogenous results. The aim of our study was to evaluate preliminary results in a small group of oral cancer patients treated by HDR BT.

Seventeen applications were performed on 16 patients in years 2001–2004, in 15 cases for new tumor (mobile tongue 10x, floor of mouth 2x, lip 3x) and in 2 cases for local recurrence after radiotherapy. Ten treatments (for T1-2N0 tumors and recurrences) were performed with brachytherapy alone (18 x 3 Gy twice daily), seven patients (T2-3 N0-2 tumors) were treated with a combination of external beam radiotherapy (40–68 Gy) and brachytherapy (2–6 x 3 Gy twice daily). The plastic tubes technique was used for brachytherapy. Follow-up periods were between 8–46 months (median 17).

Fifteen patients were disease free during follow-up period. One patient (brachytherapy alone for T2N0M0 mobile tongue cancer) died immediately after neck dissection for the neck recurrence due to the heart failure. The other one died due to distant metastases but without local recurrence. Acute complications were mucositis gr. II at maximum, late complications were ulcer of soft tissues in 3 and superficial bone necrosis in 2 cases. The evaluation of the brachytherapy implants was done according ICRU 58 recommendations.

Hyperfractionated high dose rate brachytherapy alone or as a boost to external beam radiotherapy is feasible with promising local control. Carefull planning of the implant and mandibular shielding are necessary to avoid complications.

Key words: oral cancer, high-dose brachytherapy

Both surgery and radiotherapy may be used for the treatment of oral tumors. Radiotherapy can be administered in the form of external beam irradiation (EBRT) or brachytherapy (BT). Brachytherapy brings the radiation sources directly into the tumor, allows to deliver higher doses to the target volume in shorter overall treatment time, prevents reproliferation of the tumor cells and reduces the volume of irradiated healthy tissues in comparison with EBRT. The tumor control is improved and postradiation xerostomia and soft tissue fibrosis are less frequent. BT is as effective as surgery for the treatment of the tumor with better functional and cosmetic results in majority of cases.

Most experience with BT in oral cancer was achieved with the manual afterloading technique and iridium wires with continous low dose rate (LDR) irradiation. High dose rate (HDR) afterloading devices have replaced LDR brachytherapy in many radiotherapy departments. HDR is often considered to be dangerous for interstitial implants because of higher risk of complications. Data available from literature regarding HDR BT of oral cancer are scarce with controversial results.

The aim of our retrospective study was to evaluate the technical aspects and preliminary results in a small group of patients treated in our institution by HDR BT used as a sole treatment or as a boost to EBRT.

Patients and methods

Patients. There were 17 HDR applications performed on 16 patients with histologically proved squamous cell oral carcinoma at the Dep. of Oncology and Radiotherapy, Charles

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University Hospital Hradec Králové in years 2001–2004. Thirteen patients were male and three were female, the age range was 30–77 years (median 57). Ten cases were treated for the primary tongue carcinoma, 2 cases for the floor of mouth cancer and 3 cases for lip cancer. In one case the HDR BT was applied for recurrence cancer of the lip (T3N0) after external beam radiotherapy and HDR BT boost. In the other one the HDR BT was indicated for recurrence after EBRT for the tongue cancer (T4N2M0). Follow-up periods were between 8–46 months (median 17 month) since BT. The follow up consisted of clinical examination and ultrasound of the neck in 3 months intervals and chest X ray examination once per year.

Treatment. The tumor excision with histologically negative or microscopically positive margins was performed in 10 patients with tongue cancer and biopsy only was done in the rest of patients. Neck dissection was not performed in any patient.

The treatment policy was to use HDR BT as a sole treatment in patients with T1-T2N0 tumors and in patients treated for recurrence after previous radiotherapy. The brachytherapy was used as a boost to the EBRT in patients with T3 tumors and/or with clinically positive neck nodes. The brachytherapy was also combined with elective external beam neck irradiation in 2 patients with clinically negative neck nodes. The first case was a patient 30 years old with G3 tumor and the second was patient with G2 tumor, thickeness of 10 mm and miroscopically involved excision margins. In both cases we were afraid of biological aggressivenes of the tumor and its possible microscopic lymphatic spread. EBRT was performed on linear accelerator 6 MeV with doses of 40–60 Gy. The patients and treatment characteristics are presented in Table 1.

The technique of brachytherapy. Plastic tubes technique was used for BT with spacing of 1 cm. Number of catheters was 3–8 (median 5). In 3 cases single planar and in 13 cases double planar application was used. For double planar implants, the distribution of catheters in central plane was either in equilateral triangles or in squares. Catheters were secured by plastic buttons located on the tongue surface and the submandibular region. Dose distribution was calculated using the Abacus-GammaMed planning system. Irradiation was performed with HDR device Gammamed (Gammamed, MDS Nordion Gammamed, Hahn, Germany). In our experience we had never succeeded by using the loop technique along with Gammamed, because the source was not able to go through the loop. Therefore we replaced the loop technique by catheters protruding above the tongue (Fig. 1). To insure that the top dwell position was above the tongue surface, plastic buttons of 9 mm thickness were placed at the top end of the catheter. By using a longer dwell time for the top dwell position, the tongue surface would receive an adequate dose without resorting to the use of loops. The prescription points were set at 5 mm from the catheters outside at the central plane of implant. All patients received twice daily fractions of 3 Gy with interval of at least 6 hours between fractions.

Individualized mandibular lead shielding was used in all patients except for the first 4 patients with cancer either of the

Figure 1. The technique of brachytherapy.

Table 1. The patients

Patient No	Dg	TNM	Histology/G	Surgery/Margin	Neck dissection	EBRT (Gy)	BRT (Gy)
1	Tongue	T1N0	SC/ G2	Excision/R0	0	0	18x3
2	Tongue	T2N0	SC/G2	Excision/R0	0	0	18x3
3	Tongue	T1N0	SC/G2	Excision/R1	0	0	18x3
4	Tongue	T1N0	SC/G2	Excision/R1	0	0	18x3
5	Tongue	T1N0	SC/G1	Excision/R0	0	0	18x3
6	Tongue	T1N0	SC/G1	Excision/reexcision/G0	0	0	16x3
7	Tongue	T3N2b	SC/G3	Biopsy	0	60	2x3
8	Tongue	T1N0M0	SC/G2	Excision/R1	0	50	4x3
9	Tongue	T2N1M0	SC/G2	Excision /R1	0	60	3x3
10	Floor of mouth	T2N1	SC/G2	Biopsy	0	68	3x3
11	Tongue	T1N0	SC/G2	Excision/R1	0	40	8x3
12	Floor of mouth	T2N1	SC/G2	Excision/R1	0	60	5x3
13	Base of tongue	T4N2a recurrence after EBRT	SC/G3	Biopsy	0	0	11x3
14a	Lower lip	T3N0	SC/G3	Biopsy	0	50	6x3
14b	Lower lip	reccurence after EBRT and BRT	SC/G3	Biopsy	0	0	16x3
15	Upper lip	T2N0	SC/G2	Biopsy	0	0	18x3
16	Lower lip	T2N0	SC/G2	Biopsy	0	0	18x3

SC – squamous cell carcinoma, R0 – negative margins, R1 – microscopically positive margins

tongue or floor of mouth. The details of brachytherapy are presented in Table 2.

Results

Fifteen patients were disease free for follow-up period of 8–46 months (median 17 months). One patient (No. 2) with BT alone for T2N0M0, grade 2 mobile tongue cancer recur hyperfractionation of 3 Gy twice daily relapsed in neck nodes and died immediately after neck dissection due to the heart failure. In the next case, patient with T2N1 carcinoma of the floor of mouth (No. 10) died on distant metastases (lung, bone) with local control. One patient with T3N0M0 lip cancer (No. 14a) had a local recurrence after EBRT and BT boost outside of volume of BT application and was salvaged by second BT application.

Acute complication were mucositis gr. II in most cases. We observed two cases of superfcial bone necrosis cured by sekvestrectomy (patients 1 and 11) and three cases of painless soft tissue ulcer with diameter less than 5 mm (patients 7, 8, 10) that healed up spontaneously during 2–12 months.

Both patients with osteoradionecrosis were treated without mandibular shielding. All patients with soft tissue ulcer were irradiated with combination of high doses of EBRT and brachytherapy. In addition patients 7 and 8 had nonoptimal dose distribution from the implant with low dose homogeneity index. This was caused by the small number of catheters in comparison with the large volume treated.

Three patients complained of xerostomia, all of them received EBRT. No xerostomia case was observed among patients treated by BT only.

The cosmetic results were very good (Fig. 2).

Figure 2. Cosmetic result in patient with lip carcinoma.

Table 2. Brachytherapy

Patient No	Shielding	No of catheters	No of planes	Minimum target dose (MTD)	Volume of MTD (cm^3)	Mean central dose (Gy)	V 150	Dose homogeneity index	BED10
1	0	6	2	3	16.1	3.89	8.2	77.1%	72
2	+	7	2	3	44.1	5.4	30.7	55.6%	72
3	+	8	2	3	15.4	4.25	5.8	70.5%	72
4	+	7	2	3	14.8	3.47	5.8	86.5%	72
5	+	8	2	3	13.1	4.08	6.7	73.5%	72
6	+	5	2	3	7.5	3.72	2.8	80.6%	64
7	0	4	2	3	65.7	5.8	39.3	51.7%	10.7
8	+	4	1	3	35.9	5.65	15	53.1%	16
9	+	6	2	3	15.6	3.79	6.3	79.2%	12
10	0	5	2	3	5.2	3.3	1.9	90.9%	12
11	0	5	2	3	54.8	5.5	34.2	54.5%	32
12	+	7	2	3	13.1	3.59	3.7	83.6%	20
13	+	4	2	3	9.2	3.6	3.9	83.3%	44
14a	0	3	2	3	15.0	5.4	8.6	55.6%	24
14b	0	4	1	3	10.3	3.53	3.7	85.0%	64
15	0	4	1	3	25.2	4.77	9.4	62.9%	72
16	0	2	1	3	5.6	5.9	3.1	0.51%	

V 150 – volume receiving more than 150% of MCD, BED 10 – biologically effective dose for tumor

Discussion

Surgery is often the primary treatment of oral cancer. The aim of curative surgery is to excise the carcinoma with a margin of normal tissue, but this can be often difficult. The tumor may be deeply infiltrating or have an ill-defined tumor edge with islands of tumor cells in advance of the clinical tumor edge and, making it difficult to decide where the resection margins should be placed. The more extended surgical procedure intended to achieve adequate margins may lead into impaired cosmetic and functional result. Radiotherapy may be given as the sole treatment or as an complement to surgery. It is as effective as surgery for the small tongue lesion and may be chosen as a primary treatment when surgery would result in severe disability and when clearence would be difficult to achieve. Radiotherapy may be delivered by EBRT, by radioactive implant (BT) or by combination of the two. External beam radiotherapy results in the irradiation of a large amount of surrounding normal tissue, often resulting in the short-term complication of painful mucositis and candida infections, plus the long-term complications of xerostomia, loss of taste and occasionally mandibular osteoradionecrosis.

Brachytherapy has the advantage of high radiation dose delivery to the tumor while minimizing dose delivery to the surrounding normal tissues. Brachytherapy alone allows excellent control of T1 and T2 tumors, for larger tumors must be accomplished

by EBRT, but this may be associated with soft-tissue necrosis and osteoradionecrosis.

Iridium-192 interstitial BT with low dose rate was reported as a successful treatment of oral cancer in number of large studies. In plenty of radiotherapy departments automatical HDR afterloading equipments have replaced LDR afterloading method, because of higher degree of radiation safety and practical advantages. But HDR BT is still seldom used for interstitial applications as the higher risk of complications is expected. Continuous LDR brachytherapy favors normal tissue repair during irradiation and results in benefitial therapeutic ratio between tumor control probability and normal tissue complication probability. With high dose rate brachytherapy, the DNA repair occurs only between successive fractions and therefore the gaps between fractions must be long enough, at least 6 hrs. HDR has a higher biological effect in comparison with LDR that is more profound for the normal late reacting tissues than for the tumor. The consequence is less benefitial therapeutic ratio. HDR implants must be fractionated and numerous small fractions are recommended to achieve biological equivalence with LDR brachytherapy.

There are still sparse published data reporting the use of HDR in the treatment of patients with oral cancer. Additionaly these series vary in fractionation schemes, doses and results.

UMEDA et al [1] compared the results in 25 patients with stage I–II tongue cancer treated by HDR BT with group of patinets treated with traditional LDR brachytherapy. An average dose of 59 Gy (6 Gy x 9–10 fractions/5days) was administered. Nine (36%) of 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 was significantly higher in the HDR group than in the LDR group.

LAU et al [2] reported only 53% local control rate in patients treated with HDR-BT. They treated these patients with a total dose of 45.5 Gy/7 fractions.

INOUE et al [3] 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. Five-year local control rates for LDR and HDR groups were 84% and 87% respectively. Tongue ulcer occurred in 1 patient for both groups. Bone exposure complications occured in 2 patients in the HDR group. For 1 of 2 patients with bone exposure the spacer, which recuded the dose of mandible, was not used.

YAMAZAKI et al [4] 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.

The largest series of patients with lip carcinoma treated by HDR BT was published by GUINOT et al [5]. Thirty nine patients were treated by interstitial implants to total dose of 40.5–45 Gy in 8–10 fractions. Local control was 90%. All patients developed a transitory severe mucositis, ulcerated but no active bleeding (G3), and cured in maximum of two months. There was no chronic severe complications, functional and cosmetic results were very good in most of the patients.

In our study BT alone was used for the treatment of T1,2N0M0 tumors with low risk of microscopic nodal involvement where prophylactic neck dissection or EBRT was omitted. This policy is supported even by other authors. VANDENBROUCK et al reported their randomized clinical trial of elective vs therapeutic neck dissection in epidermoid carcinoma of oral cavity [6]. They concluded that it seems posible to perform delayed neck dissection until a node is detectable. Also in the report of INOUE et al [3] most of patients with nodal metastases could be salvaged with delayed neck dissection. In our study the neck irradiation was used either in patients with clinically positive nodes or in 2 N0 patients with high risk of nodal involvement, because of jung age and poorly differentiated tumor in one case and the thickness 10 mm in the other case. The thickness of &&6 mm was significant predisposing factor for lymph node metastases in the study of YAMAZAKI et al [7].

The fractionation of HDR BT used in our group of patients, e.m. 18x3 Gy twice daily in patients treated by BT alone, differs from schedules in studies published in the literature. The theoretical reason for choice of our BT scheme was, that smaller single doses allows better therapeutic ratio bertween tumor control probability and normal tissue complication probability, which can be demonstrated by using linear quadratic model. Extrapolated response dose for late tissue are 108 Gy with 18 x 3 Gy and 180 Gy for 10 x 6 Gy. Equivalent LDR dose to the tumor are 64 Gy and 88.65 Gy, respectively (α/β for TU = 10 Gy, α/β for late tissue = 3 Gy, repair μ for TU = 1.2 h^{-1}, μ for late tissues = 0.46, repopulation k for TU = 0.3 Gy/day, k for late tissues = 0.01 Gy/day). Most of very good results with LDR BT was achieved with doses of 65–70 Gy. Also in our series the local relapse was observed only in one case (No. 14a), and was localized on the border of the implant. The node reccurence occurred in one case (No. 2), unfortunatelly heart complication after the surgery was a cause of a dead.

Superficial bone necrosis occured in 2 cases. In both the mandibular shielding was omitted, because we underestimated importance of the shielding due to our previous experience with manual LDR BT without this type of complication. The mandibular necrosis did not appear in any further patient with proper lead mold covering the alveolar ridge.

Three cases of soft tissue ulcer occured in patients treated with combination of EBRT and brachytherapy, moreover in two of them the homogeneity index of BT application was low (51.7%, 53.1%). The dose homogeneity index is defined as the ratio of Minimum Target Dose and Mean Central Dose and low values reflect high inhomogeneity of the dose distri-

bution inside of the implant with hot spots and risk of overdosage. The poor dose distribution in both patients was caused by the small number of catheters in comparison with the large volume treated.

The important advantage of BRT is sparing of salivary glands and preservation of saliva production. Non of the patients treated by BT alone suffered xerostomia, which occured in 3 of 6 patients treated by combination of EBRT and BT for tongue or floor of mouth carcinoma.

Conclusion

HDR BT alone or as a boost to EBRT with hyperfractionation of 3 Gy twice daily is feasible with promising local control. Carefull planning of the implant and mandibular shielding are necessary to avoid complications.

References

[1] UMEDA M, KOMATSUBARA H, NISHIMATSU N, YOKOO S, SHIBUYA Y et al. High-dose rate interstitial brachytherapy for the stage I-II tongue cancer. Oral surgery Oral medicine Oral pathology 2000; 90: 667–670.

[2] LAU HY, HAY JH, FLORES AD, THRELFALL WJ. 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: 19–29.

[3] INOUE T, INOUE T, YOSHUDA K, YOSHUOKA Y, SHIMAMOTO S et al. Phase III trial of high-vs low-dose-rate interstitial radiotherapy for early mobile tongue cancer. Int Radiat Oncol Phys 2001; 51: 171–175.

[4] YAMAZAKI H, INOUE T, YOSHIDA K, YOASHIOKA Y, FURUKAWA S et al. Brachytherapy for early tongue cancer: low dose rate to high dose rate. J Radiat Res 2003; 44: 37–40.

[5] GUINOT JL, ARRIBAS L, CHUST ML, MENGUAL JL, GARCIA M et al. Lip cancer treatment with high dose rate brachytherapy. Radiother Oncol 2003; 69: 113–115.

[6] VANDENBROUCK C, SANCHO-GARNIER H, CHASSAGNE D. Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of randomized clinical trial. Cancer 1980; 46: 386–390.

[7] YAMAZAKI H, INOUE T, YOSHIDA K, TANAKA E, YOSHIOKA Y et al. Lymph node metastases of early oral tongue cancer after interstitial radiotherapy. Int J Radiat Oncol Biol Phys 2004; 58: 139–146.