Journal of Radiotherapy & Medical Oncology

ORIGINAL REPORT

Brachytherapy as a Last Resort Treatment for Inoperable Tumours in Same Site Recurrence or Secondary Head and Neck Carcinomas

Anamaria Sipos[1], Laszlo Istvan[1], Edina Dordai[1], Octavian Chis[1], Gabriel Kacsó[1,2]

1) Institute of Oncology Prof. Dr. I. Chiricuta Cluj Napoca, 2) The "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj Napoca

Aim: Prospective intrainstutional evaluation of toxicity and efficacy of newly implemented interstitial high-dose-rate Iridium brachytherapy (Ir192 HDR BT) as a last resort treatment for inoperable tumours in same site recurrence or secondary head and neck carcinomas. **Material and methods:** Inclusion criteria were unifocal histologically confirmed recurrent or second squamous cell carcinoma with no evidence of nodal or distant metastasis, nor esophageal or lung synchronous cancer, tumor size and site implantable by BT and signed informed consent. From 2006 to 2009, 6 patients were included, 4 with second HNC cancers and 2 local recurrences, all having received higher than 50 Gy radiotherapy during the primary treatment. The BT dose was 39 Gy/13 fr/5days (2 or 3 fr/day at least 6 hours apart) after limited close or positive margin surgery and 55 Gy/10fr/ 10 days as sole therapy. Local control and CTCAE 3.0 acute and late toxicity were the end points. **Results**: At 30 months median follow-up, the local control was 83.34 % with 16.6 % G3 acute severe toxicity and only one case of radionecrosis, conservatively resolved. **Conclusion**: BT has definitely a role in the management of HNC, being the best choice with curative intention in selected patents with local recurrence or a second HNC in previously irradiated areas. Technical precaution should be taken to minimize the risk of radionecrosis

Key words: head and neck cancer, recurrence, salvage brachytherapy

Introduction

In stage III-IV head and neck cancer (HNC) the recurrence may be as high as 30-50% after radiation treatment (RT). There is also a risk of 20-25% for second primary upper aero-digestive tract cancers, based on the continued exposure to risk factors, mainly nicotine abuse and alcohol consumption (1) and much less to the radiation induced malignancies. The standard strategy for salvage treatment for radiation therapy failures or second primary tumors is radical tumor resection with clear resection margins. Unfortunately, clear resection margins are difficult to achieve. Therefore, there is only a slight chance of cure for these patients (2-4). The majority of these patients have previously received moderate to high doses of external beam radiation therapy (EBRT) with or without surgery or chemotherapy. Re-irradiation with EBRT, even carefully planned, is often not used because of expected high severe morbidity (5,6).

Journal of Radiotheraphy & Medical Oncology
December 2013 Vol. 19 No 2: 39-44
Address for correspondence: Gabriel Kacso
Ion Chiricuta Cancer Center
34-36 Republicii Str
400015 Cluj-Napoca, Romania
Email: gabi.kacso@gmail.com

When a limited recurrence or a new tumor develops in a previously irradiated territory, brachytherapy (BT) can deliver a curative dose with an acceptable risk of complication. This technique can be exclusive, postoperative, and applied as a local boost in combination with low doses of EBRT.

The objective of this paper is to evaluate the efficacy and toxicity of BT for patients with HNC squamous cell carcinoma, who have developed a second localization or local recurrence in a previously irradiated area.

Material and methods

This prospective study conducted between 2006-2009 at the "Ion Chiricuta" Cancer Center Cluj included only 6 patients with HNC in a previously irradiated area and treated with interstitial HDR Iridium 192 brachytherapy (BT). Criteria for eligibility were: unifocal histologically confirmed recurrent or second squamous cell carcinoma with no evidence of nodal or/and distant metastases, tumor size and site implantable for BT decided in multidisciplinary committee and signed informed consent form. All patients had undergone thorough clinical examination (including pharyngo-laryngeal/ esophagus and tracheo-bronchial endoscopy), routine blood analysis and CT scan from the base of the skull down to the upper abdomen.

Table I. Characteristics of patients included in the study.

Patients	1	2	3	4	5	6
First localization (year)	Left tonsil (2004)	Nasopharynx (1994)	Larynx (1998)	Nasopharynx (2007)	Mobile tongue (2002)	Mobile tongue (2005)
First localization - stage	T4N2bMo	T2N2Mo	T4N0M0	T4N2bM0	T2N1M0	T2N1M0
Initial treatment (surgery/CT/CRT)	CT- 4c, PF RTE 74Gy/37fr 2Gy/fr with Cis. 30mg/sqm	CT-3c, EC RTE 68Gy/34fr 2Gy/fr with Cis. 30mg/sqm	CT – 3c, C RTE70Gy/35fr 2Gy/fr with Cis. 30mg/sqm	CT-3c, EC RTE 68Gy/34fr 2Gy/fr with Cis. 30mg/sqm	Surgery pT2N1R1 RTE adj 60Gy/30fr 2Gy/fr with Cis. 30mg/sqm	Surgery pT2N2bM0 L0V0 MR neg. RTE adj 50Gy/25fr/32days 2Gy/fr with Cis. 30mg/sqm
Disease free survival	3 years	15 years	9 years	2 years	3 ½ years	9 months
Second localization (year)	Mobile tongue (2007)	Base of the tongue (2009)	Base of the tongue (2006)	Mobile tongue (2009)		
Local/ locoregional recurrence- after initial treatment (year)					local recurrence (2006) T+M0	local recurrence (2006) T+M0
Treatment for second localization	Surgery	Surgery		Surgery		
Re-stage	pT1N0M0L0V0 R1	pT1N0M0L0V0 MR<5mm	T3N0M0	pT2N0M0L0V0 R1	T2N0M0L0V0 R1	pT2N0M0 L0V0 MR <5mm
Tumor grade	unspecified	G2	unspecified	G2	G1	G1
Adjuvant BT (year)	2008	2010	2006	2009	2006	2006
BT dose Dose/fr	39Gy/13fr/5days 3Gy/fr, 2-3fr/day	39Gy/13fr/5days 3Gy/fr, 2-3fr/day	55Gy/10fr/10d 5.5Gy/fr	55Gy/10fr/10 d 5.5Gy/fr	55Gy/10fr/10 d 5.5Gy/fr	55Gy/10fr/10days 5.5Gy/fr
Number of needles	4	4	10	9	6	10
Acute toxicity	Radioepitelita G3	Radioepitelita G2 Radiodermatitis G1	Radioepitelita G2 Radiodermatitis G1 Dysphagia G1	Radioepitelita G2 Dysphagia G1	Radioepitelita G2	Dysphagia G1
Late toxicity	Xerostomia G1 Fibrosis G1	Radionecrosis G1 Xerostomia G1	Xerostomia G1	Xerostomia G1	Xerostomia G1 Fibrosis G1	Xerostomia G3 Fibrosis G2
Follow-up period	36 months	54 months	24 months	54 months	9 months	3 month
The last follow-up	LC	LC	LC	LC	regional recurrence (T0N+)	locoregional evolution (T+N+)
Treatment for local/locoregional recurrence after BT					hyperthermia	palliative chemotherapy

Legend: CT=chemotherapy; PF=5-FU with Cisplatin; CRT=chemoradiotherapy; Cis=Cisplatin; MR=resection margins; LC=locoregional control; C=Carboplatin; CRT=chemoradiation ; EBRT= external beam radiation therapy.

Of all patients included in the study, four of them were with second localization in the previously irradiated area and two with local recurrence after initial treatment. For those with the second cancer, BT was preceded by salvage surgery in 3 patients (50%), who were pT1-T2 with positive (R1) or close resection margins (MR < 0.5 cm). The fourth patient was a T3N0M0 base of the tongue, who received exclusive BT(Table I).

For the other two patients with local recurrence both initially with a mobile tongue tumor, one pT2N1R1 and the other one pT2N2bR0 treated by radical surgery and adjuvant chemoradiation full dose BT was given (table I- patients 5 and 6).

Under general anesthesia and bimanual palpation of the tumor, hollowed stainless needles were inserted through the tumor bed and surrounding tissue (target volume), replaced by polyethylene catheters fixed with bottoms (Fig 1). We used 4 to10 needles to adequately cover the tumor bed. The clinical target volume includes all visible and palpable tumor extension with a safety margin of 5 to 10 mm, depending on

the anatomical boundaries. Irradiation was done twice daily, at least 6 hours apart, with a microSelectron Nucletron machine using an 192Ir HDR afterloading source. The dose calculation was performed by the Brachytherapy Plato Planning System, using geometrical optimization (Figs. 2 and 3). The catheters were removed after the last session of brachytherapy.

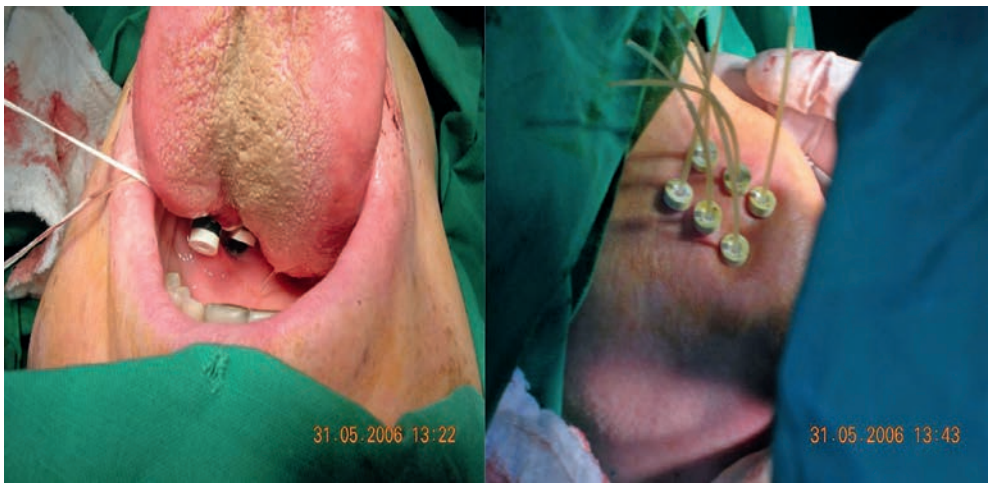

Fig. 1. Polyethylene afterloading catheters that are placed intra-operatively in the target volume and fixed with bottom, for base of the tongue second primary.

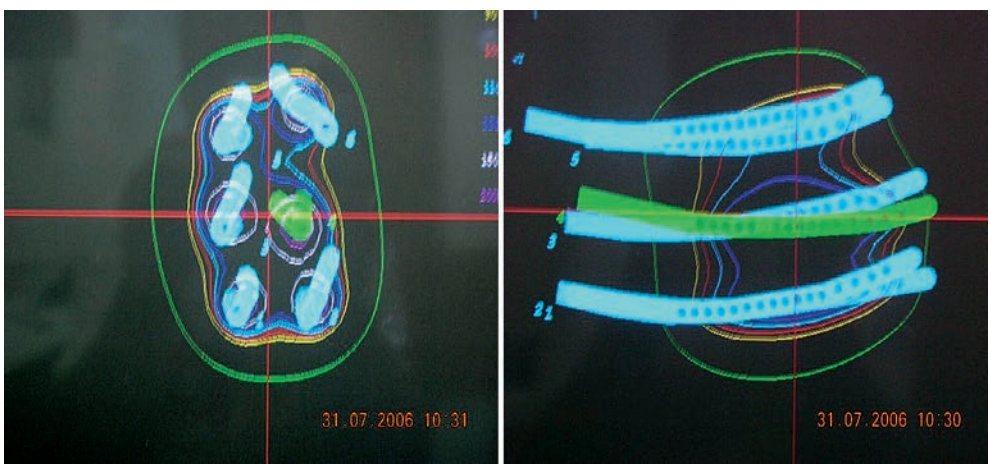

Fig. 2. Images from system planning, dosimetry corresponding to the base of the tongue cancer depicted in fig 1.

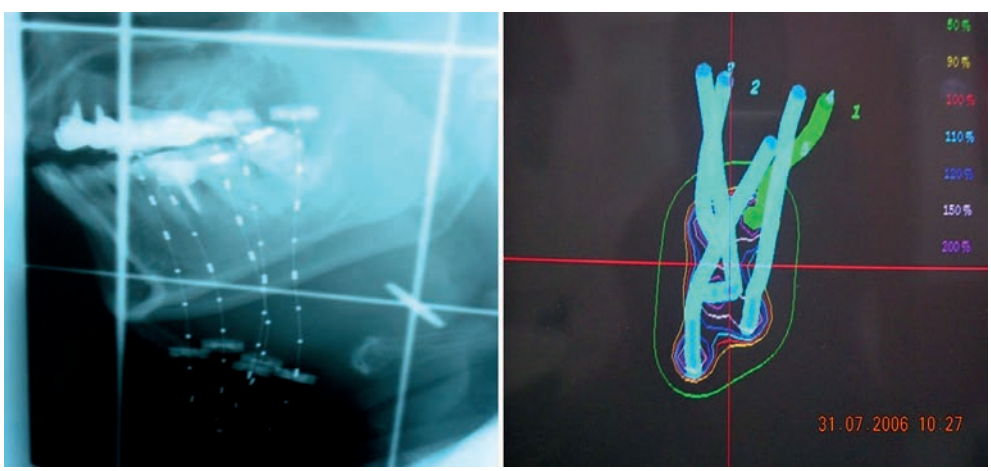

Fig. 3. Implant dosimetry for mobile tongue reccurence.

All patients were followed closely for acute/ late toxicity and local control. The primary endpoint of the analysis was the evaluation of the effect of brachytherapy on local control and the secondary endpoint was the evaluation of treatment side effects (according to the CTCAE v3.0).

Results

The median follow-up was 30 months (6 to 54 months). Patient characteristics are shown in Table II.

Three of the patients, who after the surgery were pT1-T2, followed by BT, received a total dose (TD) of 39Gy/13fr/8 days, with 3Gy/fr-2fr/day whereas 1 patient (T3 base of the tongue), and 2 with local recurrence after initial treatment got exclusive BT with a TD of 55Gy/10fr/10days.

Local control was achieved in 5 (83.34%) of a total of 6 patients. Local failure occurred in one patient who developed loco-regional disease progression after 3 months after BT, and palliative chemotherapy was administered. Another patient developed isolated regional recurrence 9 months after BT.

The most significant acute toxicity were radioepithelitis: G3occurred in one case and G2 in 3 patients (50%); radiodermatitis G1 occurred in 4 patients (66.64%) and dysphagia G1 in 2 (33.32%) of the subjects included in the study. Late toxicity was noted for 1 patient (16.66%) with radionecrosis G1, which healed with conservative treatment after 12 months. At the last follow-up 16.66% had G2 xerostomia and G2 fibrosis, and 66.64% of patients had G1 xerostomia and G1 fibrosis (Table II).

All 4 patients who developed a second location in previously irradiated areas at the last follow-up were in complete remission.

Table II. Patient characteristics and treatment outcomes.

Age	
Median	53
Range	36-76
Sex	
Male	5
Female	1
Site	
Mobile tongue	4
Base of the tongue	2
Second localization	4
Local recurrence after initial treatment	2
Initial Tumor classification	
pT1	2
pT2	3
T3	1
Initial Nodal classification	
No	1
pNo	4
pN2b	1
Resection margins	
R1	3
MR < 5mm	2
Tumor grade	
G1	2
G2	2
Unspecified	2
Prior surgery	
No (biopsy only)	1
Yes	5
Number of applicators	
Median	7
Range	4-10
Total prescribed dose (Gy)	
After surgery for pT1-T2 for 3p	39Gy/13fr/bid
Local recurrence after initial treatmen or without tumor removal – for 3 p	54-55Gy/10fr/bid
Follow-up	
Median	2.5 years
Range	6 months – 4.5 years
Local control	
T0	5
T0N+	1
T+N+	1
Acute toxicity:	
Radioepitthelitis G2/G3	3/1
Radiodermatitis G1	4
Dysphagia G1	1
Late toxicity:	
Radionecrosis G1	1
Xerostomia G1/G2	4/1
Fibrosis G1/G2	4/1

Discussions

Radiation therapy of HNC in a previously irradiated area is a complicated and risky treatment. Although it is possible to apply external beam irradiation, it is rarely used due to the modest effectiveness and high complication rates (7-9). As a result of a steep dose reduction in the neighborhood of the implant, brachytherapy offers the possibility of giving a high dose without inevitable high complication rates. In order to perform salvage therapy on patients with secondary or recurrent tumors in a previously irradiated areas careful multidisciplinary evaluation is mandatory (10,11) with documented endoscopic and cross-sectional imaging.

Both the oral cavity and oropharynx are essential in co-ordinating the complex functions of deglutition, phonation, and airway protection. Preserving this function is a difficult challenge when treating squamous cell carcinoma of this anatomical region. The treatment modalities available include surgery, external beam irradiation, brachytherapy and various combinations of them (12).The wide range of results in the literature leaves considerable uncertainty as to the treatment of choice. Despite reconstruction, resections may induce major functional deficits. Furthermore concern about adequate margins or lymph node involvement often results in the addition of postoperative irradiation, which further increases late morbidity (13,14).

Considerable experience in the treatment of HNC with radiotherapy has demonstrated that a high tumor dose is required to achieve local control. Unfortunately, even with modern imaging and new technologies such as IMRT, it is still difficult to spare adjacent normal tissues with external beam irradiation alone. Interstitial implant brachytherapy is an ideal solution if we want to deliver a high dose exclusively to the primary tumor volume there by limiting the risks of severe xerostomia or trismus (13- 16).

Some retrospective analyses compared the results of external beam irradiation followed by interstitial implant brachytherapy and primary surgery followed by external beam irradiation. A better performance status score and improved quality of life were consistently observed with BT (14, 17-20). Furthermore, it was recently clearly shown that the movement of the target caused by breathing and swallowing during external beam radiotherapy can be a drawback and should be taken into account during the delineation process (21). Brachytherapy does not confront this problem as the target is moving along with the inside implant.

With BT as a primary treatment for base of tongue cancer, a local control rate of 80-90% can be expected in T1-T2 disease and 65-80% in T3-4 lesions, with transient late necrosis of the mucosa occurring in about 25% of the cases (14, 17) whereas for mobile tongue local control rate is higher than 90% for T1/T2 N0 treated with BT alone (13, 14). It is lower in patients treated with external irradiation and a brachytherapy boost. Approximately 10-20% of patients may develop soft tissue necrosis within the implant volume. Osteoradionecrosis may occur in 5% to 10% of cases. The area of the exposed bone is usually less than 1 cm. The vast majority of necroses heal spontaneously or after medical treatment (13, 14) as happened for our single such complication.

Interstitial implant brachytherapy can also play a special role in the salvage treatment. It can be successfully used to treat tumors arising or recurring in previously irradiated territory. The 5 year local control rate is 57-69%, the 5-year overall survival rate is 14-40%, and the necrosis rate is up to 50% (4, 13, 22, 23). It should be noted that BT can be sometimes the unique curative in the intent alternative, as for base of tongue second (or even third) cancers in full dose irradiated area, which are inoperable. Even so, because of the high risk of radionecrosis, careful selection of the patients is mandatory. This explains the low number of the patients included in this study. Nevertheless, our excellent 83.3 % local control at 30 months median follow-up, together with a quite acceptable rate of toxicity authorize us to broaden the BT use as salvage treatment for inoperable in field recurrences or second head and neck carcinomas.

Conclusions

BT has definitely a role in the management of HNC, being the best choice with curative intention in selected patents with local recurrence or a second HNC in previously irradiated areas. Technical precautions should be taken to minimize the risk of radionecrosis.

References

1. Hoebers F, Heemsbergen W, Moor S, et al. Reirradiation for head-and-neck cancer:delicate balance between effectiveness and toxicity. Int. J. Radiation Oncology Biol.Phys 2011; 81: 111-118.
2. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–2098.
3. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 2003;362:933–940.
4. Strnad V, Geiger M, Lotter M, Sauer R. Role of brachytherapy for head and neck cancer: retreatment in previously irradiated area. Brachytherapy 2003;2: 158–163.
5. Nag S, Cano E, Demanes D, et al. The American Brachytherapy society recommendations for high dose rate brachytherapy for head and neck carcinoma. Int. J. Radiation Oncology Biol. Phys 2001;50:1190–1198.
6. Tan EH, Adelstein DJ, Saxton JP, et al. Concurrent chemoradiotherapy for salvage in relapsed squamous cell head-and-neck cancer. Cancer Invest 1997;15:422–428.
7. Dawson LA, Myers LL, Bradford CR, et al. Conformal re-irradiation of recurrent and new primary head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50:377–385.
8. Hwang JM, Fu KK, Phillips TL. Results and prognostic factors in the retreatment of locally recurrent nasopharyngeal carcinoma. Int JRadiat Oncol Biol Phys 1998;41:1099–1111.
9. Tan EH, Adelstein DJ, Saxton JP, et al. Concurrent chemoradiotherapy for salvage in relapsed squamous cell head-and-neck cancer. Cancer Invest 1997;15:422–428.
10. Tercilla OF, Schmidt-Ullrich R, Wazer DE. Reirradiation of head and neck neoplasms using twice-a-day scheduling. Strahlenther Onkol 1993;169:285–290.
11. Ardiet JM, Coquard R, Peiffert D, et al. Curietherapie de rattrapage des cancers ORL (cavite buccale, oropharynx, cavum). Bull CancerRadiother 1995;82:199–202.
12. Corvò R. Evidence-based radiation oncology in head and neck squamous cell carcinoma. Radiother Oncol 2007;85:156–70.
13. Mazeron JJ, Ardiet JM, Haie-Méder C, Levendag P, et all. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiotherapy and Oncology 2009;91:150–156.
14. Gerbaulet A, Pötter R, Mazeron JJ, et al. The GEC ESTRO handbook of brachytherapy. Brussels: ESTRO publisher; 2002.
15. Mazeron JJ, Noël G, Simon JM. Head and neck brachytherapy. Semin Radiat Oncol 2002;2:95–108.

Acknowledgement. This study was founded from the PN-II-ID-PCCA 2011-3.2-0414 grant(CHANCE), contract 147/2012.

No other disclosures or any conflict of interest.

16. Lapeyre M, Bellière A, Hoffstetter S, Peiffert D. Curiethérapie des cancers de la tête et du cou. Cancer Radiother 2008;12:515–21.
17. Levendag P, Nijdam W, Noever I, et al. Brachytherapy versus surgery in carcinoma of tonsillar fossa and/or soft palate: late adverse sequelae and performance status: can we obtain better sparing? Int J Radiat Oncol Biol Phys 2004;59:713–24.
18. Pernot M, Malissard L, Hoffstetter S, et al. Influence of tumoral, radiobiological and general health factors on local control and survival of a series of 361 tumors of the velo-tonsillar area treated by exclusive irradiation (external beam irradiation + brachytherapy or brachytherapy alone). Int J Radiat Oncol Biol Phys 1994;30:1021–7.
19. Mazeron JJ, Belkacemi Y, Simon JM, et al. Place of iridium 192 implantation in definitive irradiation of faucial arch squamous cell carcinomas. Int J Radiat Oncol Biol Phys 1993;27:251–7.
20. Harrison LB, Zelefsky MJ, Armstrong JG, et al. Performance status after treatment for squamous cell cancer of base of tongue-a comparison of primary radiation therapy versus primary surgery. Int J Radiat Oncol Biol Phys 1994;30:953–7.
21. Prevost JB, deBoes H, Poll J, et al. Analysis of the motion of oropharyngeal tumors and consequences in planning target delineation. Radiother Oncol 2008;87:268–73.
22. Geiger M, Strnad V, Lotter M, Sauer R. Pulsed-dose rate brachytherapy with concomitant chemotherapy and interstitial hyperthermia in patients with recurrent head-and-neck cancer. Brachytherapy 2002;1:149–53.
23. Langlois D, Hoffstetter S, Malissard L, et al. Salvage irradiation of oropharynx and mobile tongue about iridium brachytherapy in Centre Alexis Vautrin. Int J Radiat Oncol Biol Phys 1988;14:849–53.