Brachytherapy in Head and Neck Cancer: A Forgotten Art or a Skill to be Remembered!!

A.S. Kirthi Koushik* and R.C. Alva

Department of Radiotherapy, M.S. Ramaiah Medical College, Bengaluru, India

Abstract: Radiation therapy is a critical part of multi-modality management of head and neck cancers. Brachytherapy or internal radiation is an ideal method of treatment delivery to achieve the ultimate goal of radiation treatment, that is maximum dose to tumour and minimum dose to normal tissues. Brachytherapy enables the radiation oncologist to provide a perfect mixture of radiation physics, radiobiology and clinical acumen to counter head and neck cancers. Appropriate usage based on the clearly defined indications and simple methods can maximize the advantages of brachytherapy thus resulting in excellent outcomes. However, the steady decline in utilization of brachytherapy over the years coupled with the technological advances of highly conformal radiotherapy, have dented its broader application for head and neck cancers. Can the new age radiation oncologist afford to neglect this therapeutic skill set?

Keywords: Head & Neck Cancer, Brachytherapy, Radiotherapy.

INTRODUCTION

Squamous cell carcinomas of head and neck region account for more than 25% of male and more than 20% of female cancers in India. It has been postulated that there would be a substantial increase in the incidence of head and neck cancers in the coming decade amounting upto 19% of all new cases diagnosed. Estimated number of new cases by year 2020 would be 1.5 and 0.65 lakh in males and females respectively [1].

In head and neck cancers the most common sites are the Oral cavity and Oropharynx. It poses great challenges due to aggressive behavior and high rates of local, regional as well as systemic failures. The results are quite dismal even in the present day of technological advancements.

Head and Neck cancers are a broad term used to describe the tumors arising in the area that begins at the vermilion border of the lip and extends posteriorly up to the pharynx. Superiorly it is limited by the skull base and inferiorly continues into the thorax via the cervical structures. Most of the tumors of head and neck region arise from the mucosal lining and often are drained by a complex and extensive system of lymphatics associated with collateral drainage.

The natural history of disease in head and neck cancer is poorly understood but there is sufficient data to suggest that the most important mode of failure is either local or regional. Issues to consider while treating these cancers are: “to treat or not to treat”; “What is the ideal modality”; “Is it cost effective”; “Do treatments add toxicity and suffering without any significant benefit”. Kowalski *et al.* has published data to suggest and answer the first issue of treatment as the median survival for untreated head and neck cancer is just 3.82 months [2]. In today’s era, combined chemo-radiation with or without surgery can be considered as a very essential aspect of multi-modality management of most head and neck cancers. With regards to radiotherapy, external radiation has advanced by leaps and bounds in the last two decades, enhancing its applicability in various clinical scenarios. However, brachytherapy (internal radiation) advances though not too far behind, have not resulted in similar clinical utility. Brachytherapy, in a suitable patient, would be an ideal method of radiation delivery as it is a perfect mixture of physics, biology and clinical acumen thus achieving the ultimate goal of radiation therapy i.e., maximum dose to tumor and minimum dose to normal tissues in effect ensuring a higher therapeutic ratio.

HISTORY AND EVOLUTION

Historically, brachytherapy has been defined as placement of sealed radioactive sources into or in close proximity to the tumor but contemporary brachytherapy involves placement of applicators (needles/tubes) into or in close proximity to the tumor and utilization of these for placement of radioactive source thus avoiding exposure to personnel.

Brachytherapy is one of the important weapons in the armory of a radiation oncologist in his fight against head and neck cancer especially in this era of organ preservation, where one of the goals of treatment is improved quality of life. Given the complex nature of

*Address correspondence to this author at the Department of Radiotherapy, M.S. Ramaiah Medical College, MSRIT Post, M.S.R. Nagar, Bengaluru - 560054, Karnataka, India; Tel: 09901845412; E-mail: kirthi.koushik@gmail.com

ISSN: 1927-7210 / E-ISSN: 1927-7229/17

head and neck anatomy and also the pattern of recurrences in head and neck malignancy it is of paramount importance to achieve excellent loco-regional control which is vital to achieve the ultimate goals of therapy. Brachytherapy helps to achieve higher therapeutic ratio while patient stands to gain functionally, psychologically and cosmetically.

The history of brachytherapy is as old as the discovery of Radium in 1898 when both radium and radon implants were performed. In 1904, Wickham and Derais used sharpened goose quills to perform intratumoral implantations. Abbe and Morton are the first few people who have reported anecdotal reports for cure in head and neck cancers. Later different systems evolved from Manchester to present day computer based system [3].

Radiation Physics In High Dose Rate (HDR) Brachytherapy

Brachytherapy treatment outcome is affected by:

1. The particular system used for source distribution in the target volume.
2. Algorithm used for calculation of dose distribution.
3. Methods used for the determination of the strength of the radioactive source.
4. Dose rate and prescribed dose used in treatment.

The detailed description of these entities have been elaborately put forth by many task groups [4] and is beyond the scope of this article. The different technical aspects of head and neck brachytherapy has been briefly described in Table **1**.

Radiobiology of HDR Brachytherapy

Knowledge of radiobiological principles is essential to the brachytherapist. However, proper application of radiobiological principles or dose & dose rate effects cannot replace an improper implant. Function of radiobiology in general is to

1. Provide information on biologically equivalent temporal patterns of dose delivery (very much applicable for high dose rate brachytherapy)

Table 1: Technical Aspects of Head & Neck Brachytherapy

LOADING	PRELOADED	Use of radioactive needles directly and not in use now
	AFTER LOADING	Insertion of non-radioactive applicators and later loaded with radioactive sources
DURATION	PERMANENT	Common sites: prostate, thyroid Sources left in tissue Source with short half life are used Egs: Iodine, Palladium, Gold
	TEMPORARY	Common sites: head and neck, pelvis Source used for a specific time duration Used in remote afterloading machines Egs: Iridium, Cobalt
DOSE RATE	LDR	LOW DOSE RATE - 0.4Gy to 2Gy/hr
	MDR	MEDIUM DOSE RATE - 2 Gy to 12Gy/hr
	HDR	HIGH DOSE RATE - >12Gy/hr
SOURCE POSITION	INTERSTITIAL	Source within or in close proximity to tumor Egs: Tongue, Buccal Mucosa
	INTRACAVITARY	Source placed in the cavity / space Egs: Nasopharynx
	MOULD	Source placed on the surface Egs: Lip, Skin
	ENDOVASCULAR	Source in blood vessels like carotids Egs: Carotid stenosis
TECHNIQUES	GUIDE GUTTER	Classically consisted of preloaded sources. These were followed historically but not in clinical usage in the present era.
	DIRECT IMPLANTATION	
	HYPODERMIC NEEDLE	
	THREAD	
	PLASTIC TUBE	Currently employed technique.

2. Quantify effect of radiation quality.

3. Guide the implementation of biological based optimization algorithm.

Biological effects of radiation are strongly dependent upon the rate of dose delivery. Repair, Repopulation and Reoxygenation are the main factors determining outcome. These however take place between consecutive fractions, provided the interval is adequate. Lower the dose rate, higher the chances of normal tissue repair and hence in HDR brachytherapy, an inter-fraction interval of a minimum of six hours is essential for this to take effect. With regards to repopulation, clear evidence suggests improved tumour control & survival if radiation is given in shorter overall treatment time. Also, HDR brachytherapy allows for tumour shrinkage between fractions to result in reoxygenation of hypoxic cells [5]. With regards to dose and dose rate effects of HDR brachytherapy, GEC-ESTRO recommends that a smaller dose per fraction may reduce tissue injury, but a higher number of fractions would be required. Doses between 3 and 4 Gy per fraction have been recommended [6].

Brachytherapy from a Clinician's Point of View

A. Indications & Contraindications

Brachytherapy may be used as a sole modality or as boost following external radiotherapy in some sites of head and neck cancer which are accessible. The site based indications for brachytherapy in both these settings have been described in Table **2**. The use of brachytherapy alone, especially in oral tongue and floor of mouth subsites, is diminishing due to the higher possibility of lympho-vascular space invasion (LVSI) that could result in increased loco-regional failures.

Certain grey areas, such as node positive disease, post flap reconstruction of tumour bed and patients having undergone neoadjuvant therapy, could result in wrongful estimation of implant volume which could impact on outcome and toxicity. However, with proper pre-treatment evaluation, assessment of operative notes and detailed discussion with surgeons, brachytherapy can still be an excellent modality to use especially in residual/recurrent/re-irradiation setting.

The traditional contra-indications of brachytherapy are not as absolute as they used to be, as the applicators, imaging, planning and delivery systems have all been improved upon to counter these potential problems. However, clinicians need to be aware of them to be able to make relevant decisions.

B. Advantages & Disadvantages

Head and neck brachytherapy has several advantages, whenever it is feasible, as has been detailed in Table **3**. As an established treatment in

Table 2: Indication & Contra-indications for Head & Neck Brachytherapy

TUMOR SITE	BRACHYTHERAPY ALONE	BRACHYTHERAPY AS A BOOST	GREY AREA
LIP	T1,T2 & Node Neg.	T3/T4 & Node Neg.	• N+ Disease • Post – Reconstruction • Neoadjuvant therapy • Submucous fibrosis • Difficult access
ORAL TONGUE	T1 & Node Neg.	T2,T3/T4 & Node Neg.	
FLOOR OF MOUTH	T1, T2 & Node Neg.	T3/T4 & Node Neg.	
BUCCAL MUCOSA	T1, T2 & Node Neg.	T3/T4 & Node Neg.	
OROPHARYNX	Cannot be done [NA]	T1,T2 & Node Neg.	
NASOPHARYNX	Cannot be done [NA]	T1&T2 DISEASE	

Brachytherapy can be done in Recurrent, Residual and Re-irradiation setting.
Relative contraindications: Trismus, Proximity to bone, Abnormal bleeding parameters, Medically unfit, Difficult intubation and Multiple sub-site involvement.

Table 3: Advantages and Dis-Advantages of Head and Neck Brachytherapy

ADVANTAGES	DISADVANTAGES
Accuracy and precision of delivery of radiation	Accessibility an issue
Rapid dose falloff thus sparing normal tissues	Subjective as quality of implant is dependent on the radiation oncologist
High tumour bed dose hence higher cure rates	
Better therapeutic ratio	Invasive procedure
Lower integral dose	
Cosmesis better with organ preservation	
Setup uncertainties are eliminated	
Treatment interruptions due to toxicity are not there at all	

head & neck cancers, this is the only modality which when appropriately utilized provides excellent cure rates with provision for near total sparing of normal structures (rapid dose fall-off), good cosmesis (organ preservation) along with the obvious radio-biological advantages (best therapeutic ratio).

Inadequate mouth opening & hard post operative induration of the tumour bed could make the procedure difficult to perform, especially in subsites which are tougher to access. This could also impact the quality of implant. These aspects tend to improve with experience and in higher volume centers wherein emphasis is put on proper patient selection.

The biggest hindrance for its use is the clinicians reluctance, stemming from the lack of experience and fear of procedural complications. This seems to be a systemic problem which could be addressed by inculcating resident training programs as well as hands on workshops in this area.

C. Selection of Patients and Steps Involved

Here we have taken an example of brachytherapy for a case of well lateralized carcinoma tongue and the general steps involved have been illustrated.

i. Ideally when patients are to be considered for any form of radiotherapy, radiation oncologists must be involved from the outset for decision making. More so when brachytherapy is being planned, as identifying exact location of disease with extensions & other procedure related technicalities need to be verified. Magnetic resonance imaging (MRI) does provide crucial data in terms of exact soft tissue extensions to enable an objective decision on feasibility of procedure.

ii. In a de-novo case of head and neck cancer look for – mouth opening & hygiene; clearence for nasotracheal intubation; accessibility of lesion with margins for brachytherapy; feasible technique that can be applied; probable side effects that can be encountered & possible long term complications, if any.

iii. Once decided for brachytherapy, pre-procedure orders can include oral cleansing rinses & steorids/antibiotics on procedure day.

iv. Nasotracheal intubation is done and throat pack can be used if needed. Also a naso-gastric tube is passed for later use.

v. Positioning the patient is an important step. Ideally hyper-extension of the neck with optimum exposure is attempted. To achieve this shoulder roll and head ring can be used.

vi. Another pre-requisite is adequate mouth opening which can be enhanced with the use of dental separators/bite blocks.

vii. After painting/draping, examination under anaesthesia is done to estimate the volume to be implanted. Markings over the skin can be made to assist in implantation.

viii. A tongue tie is applied in the to stabilize the organ.

ix. Needles are passed percutaneously starting posteriorly, close to the angle of mandible. Needles are placed in two to three planes, lateral to medial, as per need (Figure **1**).

Figure 1: Percutaneous needle placement through the submental region.

x. Once needles are placed, interstitial plastic tubes [with closed end caps] can be threaded through them and fixed with buttons/rubber stoppers at the skin surface (Figure **2**).

xi. Tubes are cut at the pre-requisite length, numbered and implant is fastened to skin (Figure **3**).

xii. Once patient stabilizes, he is shifted to radiology, where planning Computed Tomography (CT)

scan with 1-3mm slices is done encompassing the implant with a margin. To identify the tubes on the CT scan, x ray marker wires are placed in them.

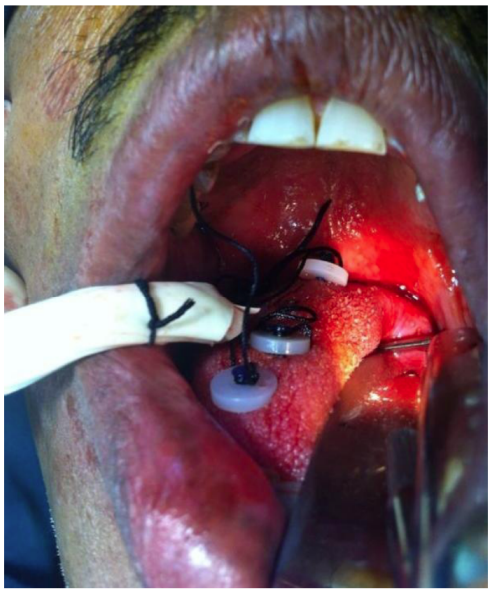

Figure 2: Intra-oral appearance of implanted plastic tubes with closed end caps.

Figure 3: Plastic tubes fastened to the skin using buttons.

xiii. In the treatment planning system, tubes are first digitized using the xray markers. A specific clinical tumour volume (CTV) of around 5 to 10mm can be defined by the oncologist (however the tubes usually define the volume to be treated) (Figure **4**). A treatment length is then defined to cover the volume of interest and then dose optimization is achieved using the planning system attributes.

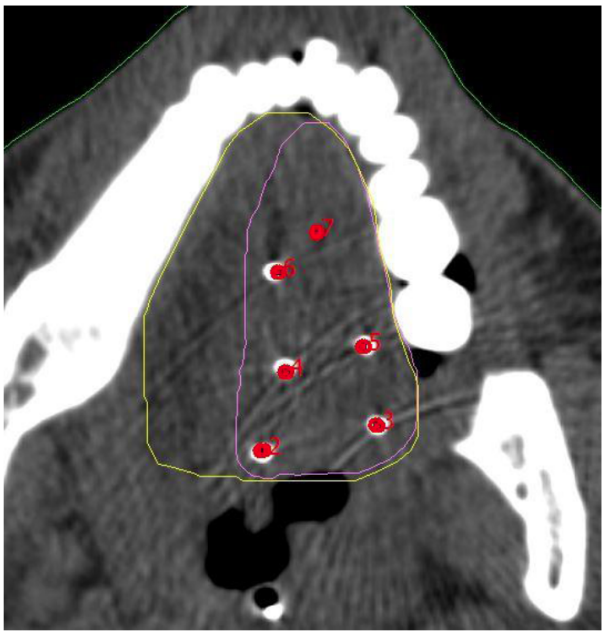

Figure 4: An axial slice of planning CT scan showing tumour volume (pink) and six digitized plastic tubes.

xiv. Doses of 3 - 4Gy per fraction is prescribed, delivering upto 10-12 fractions for primary treatment and limited to 6-8 fractions for boost treatment. Usually given as two fractions per day with a minimum of six hours gap between fractions, over 3 to 5 days.

xv. Modern treatment planning system allows to adjust dwell times and allow for dose optimization to improve tumour volume coverage as well as reduce doses to normal tissues (Figure **5**).

xvi. Once plan is accepted, the plastic tubes are connected to source transfer tubes of a multi-channel remote after-loading HDR brachy-therapy unit for execution of treatment (Figure **6**).

xvii. During removal, rarely profuse bleeding may occur. As a precaution keep clotting/thrombotic agents at hand and always maintain a patent intravenous line to manage any untoward complication.

xviii. Once stabilized, patient is kept under a short period of observation for any latent hemorrhagic episodes (rare) and started on cleansing mouth washes. Usually discharged with antibiotics and analgesics, as per requirement.

Figure 5: Dose prescription/optimization to cover tumour volume (pink) and avoid normal tissues (mandible).

Figure 6: Transfer tubes connected to catheters for treatment delivery using remote after-loading HDR brachytherapy unit.

D. Results With Brachytherapy In Different Sites

Contemporary studies on use of brachytherapy in different subsites of head and neck cancers have shown excellent local control rates across all stages of the disease. When used as a sole modality (Table **4**), it provides good local control rates with acceptable toxicity. However, oncologists are becoming more weary of using brachytherapy as a sole modality in head and neck cancers due to possibility of higher chances of LVSI resulting in higher regional recurrences. However, if patient has been appropriately selected, it still remains an excellent option.

Studies reveal that when used as a boost to external beam radiotherapy (Table **5**) or as a salvage therapy in residual/recurrent setting (Table **6**), brachytherapy has given acceptable, comparable and in some scenarios better results than other available therapeutic options. The toxicity profile too seems to be favorable, with more recent studies indicating lesser grades of reactions as well as fewer instances of complications.

E. Complications

As there has been a multitude of technological advancements, the complications profile has improved with lesser rates as well as degrees of toxicity. Toxicity profiles in most studies (Tables **4** & **5**) were similar between LDR & HDR brachytherapy arms. Higher toxicity seen when dose per fraction prescribed was higher (≥6Gy/fraction). The commonly reported complications were -

Acute: Bleeding, pain at implant site, infections, mucositis

Sub acute: soft tissue/track necrosis, fibrosis, worsening of trismus, depigmentaion

Late: Osteoradionecrosis (rare)

Has Conformal Radiotherapy Diminished the Role of Brachytherapy?

Highly conformal radiotherapy techniques, over the last few years have provided oncologists with excellent options to selectively escalate dose to gross disease areas in head and neck cancer with minimal normal tissue toxicity profile. Issues pertaining to patient positioning & daily treatment reproducibility also have been addressed with the modern image guidance techniques. Brachytherapy, which has taken the back seat due to these developments, is still an effective tool in selected cases wherein the oncologist is certain of the volume being treated and can expect a radio-biological advantage as well as superior therapeutic outcome. In a recent paper, Orton *et al.* assessed the Surveillance, Epidemiology and End Results (SEER) database between 1973 to 2012 on patterns of radiotherapy usage in oral cavity tumours [25]. They find that in matched patients, use of brachytherapy boost in the definitive management of these cancers gives a statistically significant overall survival advantage(median OS - 2.4yr vs 1.4yr). However, they

Table 4: Results of HDR Brachytherapy Alone

Author	Site (N)	HDR dose	Results	Toxicity
Inoue (2001) [7]	Tongue (25)	60 Gy / 10 # / 1 week	4 yr LC – 87%	8% - B; 4% - S
Lueng (2002) [8]	Tongue (19)	55 Gy / 10 # / 6 days	5 yr LC – 94.7%	5% - S & B (GrII)
Guinot (2003) [9]	Lip (39)	40.5 – 45 Gy / 8 -10 # / 5 -7 days	5 yr LC – 88%; CSS - 90%	NA
Yamazaki (2003) [10]	Tongue (58)	48 – 60 Gy / 8-10 # / 6 -7 days	5 yr LC – 84%	3% - B; 3% - S
Umeda (2005) [11]	Tongue(26)	6Gy x 9-10Fr	5yr OS - 53%-72%	NA
Kakimoto (2006) [12]	Tongue (71)	54 – 60 Gy / 9 -10 # / 5 -7 days	5 yr LC – 85.9%; OS - 80.3%	13% - S; 14% - B
Ghadjar (2012) [13]	Lip(33)	Median 36Gy	5yr OS - 53%-77%	0%
Mohanti (2014) [14]	OC(84)	40Gy/9-10Fr	5yr DFS-52%	23% GrII S

LC - Local Control; OS - Overall Survival; DFS - Disease Free Survival; CSS - Cause Specific Survival; S- soft tissue related; B - Bone related.

Table 5: Results of HDR Brachytherapy as Boost

Author (Yr)	Site (N)	EBRT	HDR Dose	Results	Toxicity
Kakimoto (2003) [15]	Tongue (14)	12.5 – 60 Gy	32 – 60 Gy / 8 -10# / 5 - 7 days	5 yr LC - 71%	21% - S; 0% - B
Nose (2004) [16]	Oropharynx (82)	46 Gy	21 Gy / 3.5 # / 2 days	2 yr LC 89% (T1/2); 66% (T3/4) 2 yr OS : 88% (T1/2); 64% (T3/4)	29% - S (transient)
Nagy-Takacsi (2004) [17]	Base Of Tongue (37)	60 Gy (median)	18 – 28 Gy	5 yr LC - 60%; OS - 46%	3% - S; 1% - B
Chen (2006) [18]	Oropharynx (90)	50 Gy	24 Gy (median)	5 yr LC - 83% - 64% (T1 -T4) 5 yr OS 55%	14% overall
Kotsuma (2008) [19]	Oral Cavity(14)	40 - 50Gy	24 – 60Gy (median 48Gy)	5 yr LC - 80%	0%

LC - Local Control; OS - Overall Survival; S- soft tissue related; B - Bone related.

Table 6: Results of HDR Brachytherapy for Recurrence or Reirradiation

Author	Site (N)	HDR dose	Results	Toxicity
Krull (1999) [20]	HNC (19) - Rec/PD	10Gy once a week x 3	2yr LC - 34%	5% S
Glatzel (2002) [21]	HNC (90) (Recurrent/residual)	5 to 42Gy	1yr - 28%-84%	6.7% GrIII
Narayana (2007) [22]	HNC (30)	3.4Gy x 10; 4Gy x 5(boost)	2yr LC - 71%	6 GrII/4 GrIII
Schiefke (2008) [23]	HNC (13)	3Gy x 10Fr(boost)	2yr LC - 80%	S - 8%; B - 15%
Bartochowska (2012) [24]	HNC (50) (Recurrent)	12-30Gy/3-10Fr	1yr-28%-40%	35%

LC - Local Control; S- soft tissue related; B - Bone related.

also find a steady decline in the utilization of brachytherapy over four decades by almost 0.58% per year overall. This has been attributed to many possible reasons, of which the preference of highly conformal radiotherapy & reluctance to use brachytherapy are the two most important causes.

CONCLUSIONS AND FUTURE DIRECTIONS

At the beginning of the review we had set a few questions that need to be answered and the probable answers are as below:

- There is a need to treat all malignancies of Head and Neck origin.
- Brachytherapy seems to be an ideal modality wherever feasible & is cost-effective
- Brachytherapy doesn't add to toxicity, instead provides better control/cure rates.
- Brachytherapy with intensity modulation may be the thing for the future.

The biggest obstacle for the use of head and neck brachytherapy in ideally selected patients is the reluctance of oncologists to perform the implant due to apprehension & lack of experience. Directed teaching programs and hands-on workshops would help in transforming this "forgotten art" of the previous generation to a "necessary skill" to be imbibed by the new age oncologist for adequate management of head and neck cancers.

ABBREVIATIONS

HDR	=	High Dose Rate
MDR	=	Medium Dose Rate
LDR	=	Low Dose Rate
GEC-ESTRO	=	Groupe Européen de Curiethérapie-European Society for Radiotherapy & Oncology
LVSI	=	Lympho-Vascular Space Invasion
MRI	=	Magnetic Resonance Imaging
CT	=	Computed Tomography
CTV	=	Clinical Tumour Volume
Gy	=	Gray
Fr	=	Fraction
LC	=	Local Control
DFS	=	Disease Free Survival
OS	=	Overall Survival
CSS	=	Cause specific Survival
Gr	=	Grade
HNC	=	Head Neck Cancer
hr	=	hour
Neg.	=	Negative
NA	=	not applicable
SEER	=	Surveillance, Epidemiology and End Results

REFERENCES

[1] Takiar R, Nadayil D, Nandakumar A. Projections of Number of Cancer Cases in India (2010-2020) by Cancer Groups. Asian Pacific J Cancer Prev 2010; 11: 1045-1049.

[2] Kowalski LP, Carvalho AL. Natural history of untreated head and neck cancer. Eur J Cancer 2000; 36(8): 1032-1037. https://doi.org/10.1016/S0959-8049(00)00054-X

[3] Kovács G. Modern head and neck brachytherapy: from radium towards intensity modulated interventional brachytherapy. J Contemp Brachytherapy 2015; 6(4): 404-416.

[4] American College of Radiology. ACR–AAPM technical standard for the performance of high dose-rate brachytherapy physics. Available at www.acr.org/~/media/EF9F4CCED3C5426B915BC2C91974CE5. 2015.

[5] Mazeron JJ, Scalliet P, Van Limbergen E, Lartigau E. Radiobiology of brachytherapy and the dose-rate effect. A. Gerbaulet, R. Pötter, J.J. Mazeron, H. Meertens, E. Van Limbergen, editors. In: The GEC-ESTRO handbook of brachytherapy. ESTRO, Brussels 2002; 95-121.

[6] Mazeron JJ, Ardiet JM, Haie-Méder C, Kovács G, Levendag P, Peiffert D, *et al*. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiother Oncol 2009; 91(2): 150-6. https://doi.org/10.1016/j.radonc.2009.01.005

[7] Inoue T, Inoue T, Yoshida K, Yoshioka Y, Shimamoto S, Tanaka E, *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: 171-5. https://doi.org/10.1016/S0360-3016(01)01561-9

[8] Leung T, Wong VY, Kwan K, Ng T, Wong C, Tung SY, *et al*. High dose rate brachytherapy for early stage oral tongue cancer. Head Neck 2002; 24(3): 274-81. https://doi.org/10.1002/hed.10021

[9] Guinot J, Arribas L, Chust ML, Mengual JL, García Miragall E, Carrascosa M, *et al*. Lip cancer treatment with high dose rate brachytherapy. Radiother Oncol 2003; 69: 113-5. https://doi.org/10.1016/S0167-8140(03)00271-8

[10] Yamazaki H, Inoue T, Yoshida K, Yoshioka Y, Furukawa S, Kakimoto N, *et al*. Brachytherapy for early oral tongue cancer: low dose rate to high dose rate. J Radiat Res 2003; 44: 37-40. https://doi.org/10.1269/jrr.44.37

[11] Umeda M, Komatsubara H, Ojima Y, Minamikawa T, Shibuya Y, Yokoo S, *et al*. A comparison of brachytherapy and surgery for the treatment of stage I-II squamous cell carcinoma of the tongue. Int J Oral Maxillofac Surg 2005; 34: 739-44. https://doi.org/10.1016/j.ijom.2005.02.015

[12] Kakimoto N, Inoue T, Inoue T, Murakami S, Furukawa S, Yoshida K, *et al*. High-dose-rate interstitial brachytherapy for mobile tongue cancer: influence of the non-irradiated period. Anticancer Res 2006; 26: 3933-7.

[13] Ghadjar P, Bojaxhiu B, Simcock M, Terribilini D, Isaak B, Gut P, *et al*. High dose rate versus low dose-rate brachytherapy for lip cancer. Int J Radiat Oncol Biol Phys 2012; 83(4): 1205-12. https://doi.org/10.1016/j.ijrobp.2011.09.038

[14] Mohanti BK, Sahai P, Thakar A, Sikka K, Bhasker S, Sharma A, *et al*. Institutional Experience of Interstitial Brachytherapy for Head and Neck Cancer with a Comparison of High- and Low Dose Rate Practice. Asian Pac J Cancer Prev 2014; 15(2): 813-818. https://doi.org/10.7314/APJCP.2014.15.2.813

[15] Kakimoto N, Inoue T, Inoue T, Murakami S, Furukawa S, Yoshida K, *et al*. Results of low- and high-dose-rate interstitial brachytherapy for T3 mobile tongue cancer. Radiother Oncol 2003; 68: 123-8. https://doi.org/10.1016/S0167-8140(03)00055-0

[16] Nose T, Koizumi M, Nishiyama K. High-dose-rate interstitial brachytherapy for oropharyngeal carcinoma: results of 83 lesions in 82 patients. Int J Radiat Oncol Biol Phys 2004; 59: 983-91. https://doi.org/10.1016/j.ijrobp.2003.12.015

[17] Takácsi-Nagy Z, Polgár C, Oberna F, Somogyi A, Major T, Remenár É, *et al*. Interstitial high-dose-rate brachytherapy in the treatment of base of tongue carcinoma. Strahlenther Onkol 2004; 180(12): 768-75. https://doi.org/10.1007/s00066-004-1238-x

[18] Chen J, Pappas L, Moeller JH, Rankin J, Sharma PK, Bentz BG, *et al*. Treatment of oropharyngeal squamous cell carcinoma with external beam radiation combined with interstitial brachytherapy. Head Neck 2007; 29(4): 362-9. https://doi.org/10.1002/hed.20528

[19] Yamazaki H, Yoshida K, Yoshioka Y, Shimizutani K, Furukawa S, Koizumi M, *et al*. High dose rate brachytherapy for oral cancer. J Radiat Res 2013; 54(1): 1-17. https://doi.org/10.1093/jrr/rrs103

[20] Krüll A, Friedrich RE, Schwarz R, Thurmann H, Schmelzle R, Alberti W. Interstitial high dose rate brachytherapy in locally progressive or recurrent head and neck cancer. Anticancer Res 1999; 19(4A): 2695-7.

[21] Glatzel M, Buntzel J, Schroder D, Küttner K, Frohlich D. High-dose-rate brachytherapy in the treatment of recurrent and residual head and neck cancer. Laryngoscope 2002;112; 8(1): 1366-71.

[22] Narayana A, Cohen GN, Zaider M, Chan K, Lee N, Wong RJ, *et al*. High-dose-rate interstitial brachytherapy in recurrent and previously irradiated head and neck cancers – preliminary results. Brachytherapy 2007; 6(2): 157-63. https://doi.org/10.1016/j.brachy.2006.12.001

[23] Schiefke F, Hildebrandt G, Pohlmann S, Heinicke F, Hemprich A, Frerich B. Combination of surgical resection and HDR-brachytherapy in patient with recurrent or advanced head and neck carcinomas. J Craniomaxillofac Surg 2008; 36(5): 285-92. https://doi.org/10.1016/j.jcms.2007.08.009

[24] Bartochowska A, Wierzbicka M, Skowronek J, Leszczyńska M, Szyfter W. High-dose-rate and pulsed-dose-rate brachytherapy in palliative treatment of head and neck cancers. Brachytherapy 2012; 11(2): 137-43. https://doi.org/10.1016/j.brachy.2011.09.006

[25] Orton A, Boothe D, Gan M, Monroe MM, Hitchcock YJ, Lloyd S. The "decay" of brachytherapy use in tumors of the oral cavity: A population-based patterns of care and outcomes analysis from 1973 to 2012. Brachytherapy 2016; 15(6): 851-858. https://doi.org/10.1016/j.brachy.2016.05.007

Received on 22-12-2016 Accepted on 29-12-2016 Published on 26-01-2017

https://doi.org/10.6000/1927-7229.2017.06.01.3