Review article

Is there any place for LDR brachytherapy for head and neck carcinomas in HDR era?

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Abstract

In Poland, the classical LDR brachytherapy for head and neck carcinomas with Ir-192 wires or hairpins has completely disappeared some time ago after 30 years of successful clinical use. Can this technique be fully and safely replaced by HDR or PDR application? This option seems attractive because of new possibilities of 3D reconstruction and computer real-time treatment planning and optimization. However, in my opinion, long time is needed to get a clinical and scientific experience that has been accumulated for decades with the use of LDR technique.

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Key words: LDR brachytherapy, head and neck carcinomas.

Purpose

Squamous cell carcinomas of the head and neck region are a unique challenge to the radiation oncologist because of the close relationship of various structures in the region that are responsible for maintaining the aero-digestive functions of the body along with the inherently complex topography. Brachytherapy can be delivered in several situations and in combination with other forms of therapy. In the majority of areas like the tongue, buccal mucosa and oropharynx, brachytherapy is used as an adjuvant to external beam radiation (EBRT). External radiation of 40-50 Gy is delivered over a period of 4-5 weeks followed by brachytherapy. This approach allows sterilization of microscopic cells in tissues surrounding the tumor and also reduces the tumor size in order to limit the implanted volume. The high chance of occult contralateral and ipsilateral neck node metastatsis also makes this technique a sensible procedure. However, the pretreatment volume should be clearly recorded as this volume is always implanted, regardless of the size of the tumor at the time of brachytherapy.

LDR brachytherapy still represents a well proven option as an exclusive modality treatment for early stage of head and neck tumors. Evidence points that for early and superficial lesions of the tongue or floor of the mouth, brachytherapy may provide a better cure rate with lesser toxicity as compared to EBRT alone or EBRT with brachytherapy. Local control rates can be as high as 80-90%, with minimal late toxicity. Using brachytherapy as the sole modality can almost double the local control rates for smaller lesions of the oral tongue. When LDR brachytherapy is used alone, doses of 66-70 Gy are delivered to the primary tumor (GTV) with a safety margin which includes the potential area of microscopic spread (CTV). The margins chosen vary according to location, type of tumor and personal experience, but usually margins of 1-1.5 cm are chosen with care to avoid the mandible as far as possible. Radiotherapy and surgery allows 80% of local control rate in T1-2 tumors with limited neck node involvement [1, 2]. Brachytherapy can be combined with surgery in various ways. The most common approach is a planned neck dissection after the completion of brachytherapy. This method is generally used for small lesions of the tongue or oropharynx where the risk of occult nodal metastasis may be as high as 30%.

Exclusive brachytherapy offers comparable results to surgery in terms of local control and survival in small tumors without cosmetic and functional side effects that are often carried out by surgery (Table 1). In 1987, the GEC (Groupe Europeen de Curietherapie) ESTRO, summarized treatment results of more than 2 000 cases from different European countries and demonstrated that for T1-2 lesions of mobile tongue, exclusive brachytherapy offers better local control rates than the integration of brachytherapy and EBRT [9, 10]. The possible reason could be the shortening of the total treatment time with the use of exclusive brachytherapy amplifying the biological response in the process. With this method the risk of a "geographical missing" is very low as the sources maintain fixed relationship to the target volume. In addition, it eliminates errors due to setup inaccuracies to a significant extent and thus can minimize the irradiated volume by reducing the Planning Target Volume (PTV).

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Acute radiation reaction is sharply localized and usually occurs after treatment completion, therefore the treatment interruptions due to acute reactions are uncommon and radiation morbidity is limited. In this way, better cosmetic results can be obtained due to reduced volume of tissue exposed to high dose of radiation.

The GEC-ESTRO data have been confirmed by several authors from leading institutions. A group from Paris published a retrospective analysis on 160 patients who underwent radical LDR brachytherapy for a T1-2 floor of the mouth cancer [11]. At 5 years after treatment 89% of the patients were disease-free. The rates of local tumor failure were 10% of all patients, 7% of T1 tumors, and 12% of T2. The 5-year actuarial survival rate for all patients was 76%, 88% for T1, and 74% for T2. The group from Nancy analyzed a group of 207 patients with a cancer of the floor of the mouth treated with exclusive irradiation [12]. External beam irradiation to the tumor bed and the node areas and complementary LDR brachytherapy to the primary tumor was applied in 105 cases and an exclusive LDR brachytherapy to the tumor with or without neck dissection of the node areas was delivered to the remaining 102 cases. In the first part of the study brachytherapy was performed according to the hairpin technique and later with the plastic tubes following the Parisian system. The local control rates at 5 years were 97% and 72%, respectively, for T1-2 tumors, while the 5-year specific survival rates were 88% and 47%, respectively. Authors concluded that patients treated by exclusive brachytherapy for T1-2 N0 tumors had better 5-year results (92% local control; 76% specific survival) than those treated by combined therapy (63% local control; 35% specific survival). Other authors confirmed similar rates of local control and survival [13]. Exclusive brachytherapy has been demonstrated to be effective and safe also in locations in which the treatment is technically more difficult to perform. In a series of 44 patients treated with exclusive interstitial brachytherapy for a T1 or T2 squamous carcinoma of the velotonsillar area, 5-year overall and progression-free survival rates of 76% and 68% were obtained respectively [14].

It has been proven by many authors that brachytherapy may also provide a useful method for the treatment of patients with recurrent, persistent, or the second of primary head and neck malignant tumors in a previously irradiated region. That can be considered as useful tool in addition to EBRT, surgery and chemotherapy in locally advanced T3-4 tumors.

Another aspect that has been intensely investigated was the optimal dose, dose rate, and other technical parameters in order to maximize the tumor response without raising the number of treatments complication. According to the GEC recommendations, in an exclusive LDR brachytherapy treatment for T1-2 tumors, a total dose of not more than 70 Gy with a dose rate of 0,45 to 0.6 Gy per hour should be delivered. In the opinion of some authors, a dose rate of 0.42 Gy per hour or less should be used to deliver total doses of 50 to 60 Gy [15].

With the progress of HDR treatments, a very interesting issue came into view about how the experience of LDR brachytherapy can be used for calculation of biological equivalent and safe dose in terms of normal tissue tolerance. Japanese authors compared exclusive LDR and HDR brachytherapy for T1-2 tumors of the mobile tongue [16]. In a group of 59 patients, they discovered that the 5-year local control rate was not different between the two groups (77% vs. 76%, respectively). With the higher incidence of acute adverse effects in the HDR group, no difference was confirmed regarding late toxicities. Interesting results concerning PDR brachytherapy have been reported by German authors [17]. They have analyzed retrospectively a group of 47 patients with head and neck cancers treated with BRT alone (24 patients) or BRT and EBRT (23 patients) delivered with an effective dose rate of 0.5 to 0.7 Gy per hour. The authors found that toxicity rates were comparable with LDR regimens. These data support some opinions that LDR brachytherapy for head and neck tumors can be effectively and safely replaced by HDR or PDR treatments.

Table 1. Results of exclusive LDR brachytherapy for the tongue and floor of mouth carcinoma

Authors	N =	Dose (Gy)	Local Control (%)		
			T1	T2	All
Shibuya *et al.* [3]	226	70	92	82	85
Lefebvre *et al.* [4]	341	60-70	–	–	82
Mazeron *et al.* [5]	155	60-70	87	87	87
Inoue *et al.* [6]	21	70	86	–	–
Lees *et al.* [7]	27	67	80	50	67
Pernot *et al.* [2]	70	–	–	90	–
Bachaud *et al.* [8]	26	60-70	100	70	88

Another option that can be taken into consideration is the postoperative brachytherapy. It is rarely indicated except in situation where gross residual or recurrence is documented and there are some contraindications for EBRT. The most regular clinical situation takes place after resection of a recurrent tumor in a previously irradiated area. LDR brachytherapy doses of 50 to 60 Gy have for several decades been used for the treatment of patients with recurrent head-and-neck cancer, with 30-70% salvage rate and 30-40% complication rates. For HDR brachytherapy the most frequently recommended doses range from 3-4.5 Gy per fraction in 8-18 fractions.

Technique of interstitial application for oral cavity carcinoma

According to commonly accepted rules, before implantation of the catheters, the oral cavity should be kept dry with adequate preanesthesia medication, including scopolamine and suction. The borders of the tumor should be marked with a marker such as Castellani's paint, gentian violet, or with a surgical marker. The patient's lips should be retracted and the tongue should be pulled or depressed. Then the implantation can be performed. It is important to keep in mind that the anterolateral needles of an implant of the oral cavity should be kept away from the mucosa covering the bone in the upper and lower gum, as well as

from the periosteum, teeth and bone. In order to avoid "hot spots" around each needle it is recommended to maintain the distance with the use of a regular fluoride carrier that is thickened on the inside by one to four layers (2-8 mm). In another series, 103 patients with T1 or T2 tongue carcinoma were treated by a single-plane implantation of ^{192}Ir pins [18]. Sixty of them were treated by BRT alone, and the rest of patients with external irradiation and/or chemotherapy. From this group 48 and 55 patients were given BRT with and without a spacer, respectively. The use of a spacer reduced about 50% of the absorbed dose at the lingual side surface of the lower gingival to that with the absence of a spacer. Mandibular osteonecrosis occurred in 2.1% and 40.0%, with and without a spacer, respectively ($p = 0.0004$). Due to simplicity and flexibility of this procedure, most of the modern day interstitial implants are inserted with the use of plastic catheters which are introduced under the guidance of hollow needles.

Technique of interstitial application for the tongue and floor of mouth carcinoma

Lesions beneath the tongue, or in the floor of the mouth, should be implanted through the dorsum of the tongue in case of using the standard needles. The anterolateral needles pass the tongue and are reinserted into the floor of the mouth. The implants should be extended beyond the visible or palpable tumor by at least 1 cm in all directions. If the technique of interstitial implants with nylon tubing is used for lesions of the oral tongue or floor of the mouth, a submental or submaxillary approach is preferred. The insertion of metallic guides into the oral cavity is performed with one hand. The exit points of the guides in the oral cavity are verified with the index finger of the other hand. This procedure is called "through-and-through".

The major nylon tubing is threaded through the metallic guides and looped around the dorsum of the tongue and then it exits through a parallel metallic guide. In the next step the metallic guides are pulled out externally. The nylon thread is secured by a crimp with a metallic button at one end. The procedure continues with other loops, leaving the other end open for insertion of the radioactive sources. In order to facilitate removal it is suggested to put a silk thread through the loop of each nylon tube inside the oral cavity.

The position of the sources is then verified on an X-ray films using radiopaque inactive dummy sources and finally the appropriate ^{192}Ir wires or seeds in nylon tubing are inserted. The other end of the larger nylon tube is crimped.

Implantation with rigid needles of the posterolateral border of the tongue via the oral cavity requires pulling the tongue forward in order to start the implantation at the base of the tongue. The first needle is inserted pointing inferiorly posterior at about 45 degrees; a lesser angle is used for successive needles. Eventually, the tongue returns to its normal position and the implant needles takes a vertical position.

Another technique with the ^{192}Ir hairpin was described by French authors [19]. In this procedure an inactive gutter guides were placed into the tongue, and under fluoroscopic control it was verified whether the gutter guides were parallel. The iridium hairpins were afterloaded into the guides, which were removed at that time. A suture was used to secure each hairpin to the tongue. In order to decrease the irradiation given to the mandible it is recommended to suture a cotton roll between the tongue and the mandible. This way the tongue is displaced medially. Significant effort should be made in order to reduce treatment morbidity. The risk of mandibular necrosis in patients with oral cancer treated with LDR brachytherapy is about 10% [20]. No serious incidence of this complication was observed where tumor site (mobile tongue vs. floor of mouth), dental status, or total physical dose was considered. An essential correlation between the incidence of bone necrosis and two main parameters was found, with dose rate ($p < 0.02$) and reference volume ($p < 0.05$). A threshold value may be suggested for both dose rates (0.5 Gy per hour) and reference volume (25 000 mm^3).

Interstitial application procedures for the base of tongue carcinomas

Interstitial application of catheters in the region of the base of the tongue is a difficult method that requires good medical training and adequate surgical skills. Due to tissue oedema and high risk of airway obstruction, it is highly recommended to perform an elective temporary tracheostomy before the main procedure. Implantation of the base of the tongue and the posterolateral border of the oral tongue is best to accomplish with the help of long metallic or teflon catheters with guides inserted through the submaxillary/subdigastric region. This can be done with the index finger of the other hand in the oropharynx to verify the position of the guide at the exit point of the tongue base. The nylon thread is inserted through the tubing into the oropharynx, looped around, and brought out through the opposite guide. The metallic guides are withdrawn from the submental region and the nylon tubes are secured externally with metallic buttons as described earlier. Occasionally, it is not achievable to open the oral cavity adequately. In this case it is suggested to perform a submandibular implant with metallic guides and afterloading of ^{192}Ir. Double-plane or volume implants can be performed without any difficulty. After implant localization X-ray films with dummy sources are taken. Then the ^{192}Ir wire or seeds in nylon threads are inserted into the nylon tubing or metallic guides. The next step is the calculation of isodose distributions.

Technique of interstitial application for tonsillar region and faucial arch

The implantation technique of the ^{192}Ir hairpin or plastic tube have been elaborated and ameliorated by Pierquin *et al.* [21] and Mazeron *et al.* [22]. The nylon tube technique also may be used to implant the soft palate [23]. Depending on the extent of the lesion the iridium hairpin procedure is used with one gutter guide placed in the soft palate in

the transverse plane and additional gutter guides placed vertically into the anterior tonsillar pillars. Iridium hairpins are afterloaded into the gutter guides, which are removed as described earlier. If the uvula is absorbed by the tumor, it should be amputated before implantation [24].

Recapitulation

In my opinion low dose rate brachytherapy is still considered radiobiologically superior to the other forms of brachytherapy. The reason lies in the differential repair kinetics of the tumor and the normal cells. The repair half life for normal tissues ($t_{1/2}$ = 1.5 hrs) is lesser than that for tumors, so continuous application of low dose radiation allows healing of the radiation induced subleathal damage during the course of the radiation itself. This way the therapeutic ratio between cell kill and normal tissue damage becomes more favorable. LDR brachytherapy is still considered potentially less toxic then HDR brachytherapy, when it is essential to reach the limits of the normal tissue toxicity for maximizing tumor control of – for example – definitive treatment of small lip and tongue cancers using brachytherapy as a single way of treatment. On the other hand, HDR brachytherapy allows significant flexibility in planning the procedure and as an afterloading technique it moderates radiation protection. The higher dose rate permits immediate treatment, it reduces patient discomfort and allows OPD based treatment which unlike LDR brachytherapy often takes several days. The high dose rate however, negates the biological advantage of LDR brachytherapy and therefore the treatment needs to be administered in several fractions. This way the overall treatment time is longer for the majority of head and neck cancer patients. The total dose has to be corrected and lowered in order to avoid excessive late toxicity. The exact magnitude of this correction remains an area of controversy with various authors recommending values between 45-55% of LDR doses. Another field of discussion is the dose per fraction and it has been observed that doses higher than 4.5 Gy per fraction in the head and neck region often lead to unacceptable rates of tissue necrosis. In case of using HDR brachytherapy after EBRT, the HDR doses need to be suitably corrected and the doses delivery usually vary from 40-50 Gy in 3-4 Gy per fraction, administered twice daily with a suitable interfraction interval of 6 hours or more [25-28]. Selected results of combined EBRT and HDR boost are presented in Table 2. Selected results of exclusive HDR brachytherapy in oral cavity carcinomas are presented in Table 3.

Some superficial tumors of the head-and-neck region (buccal mucosa, hard palate, oral cavity) can be treated with brachytherapy using molds. The recommended total dose (prescribed at 0.5 cm depth) in LDR brachytherapy is about 60 Gy. Brachytherapy in a dose of 15 to 30 Gy can also be applied as a boost of 45 to 50 Gy EBRT. Moulds should be prepared from a tissue equivalent material like perspex or dental acrylic.

Complications of brachytherapy depends of a significant extent on the irradiated volume and the dose inhomogenity. Transient soft tissue necrosis can be expected in 15-20% patients which usually resolves spontaneously. Mandibular osteoradionecrosis can occur in 5-10% patients. If the area of necrotic bone is up to 1 cm^2 it is usually very promising to obtain healing with conservative treatment. In contrast to EBRT the risk of neural and salivary gland toxicity is very low.

Table 2. Results of HDR brachytherapy boost after EBRT

Authors	Location	EBRT dose	HDR dose/ fractionation	Results
Kakimoto *et al.* [25]	tongue	12.5-60 Gy	32-60 Gy/ 8-10#/ 5-7 days	5 yr LC 71%
Nose *et al.* [26]	oropharynx	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)
Takásci-Nagy *et al.* [27]	base of tongue	50-60 Gy	18-28 Gy	4 yr LC 60% OS 46%
Chen *et al.* [28]	oropharynx	50 Gy	24 Gy	5 yr LC 83% 64% (T1-T4) 5 yr OS 55%

Table 3. Results of exclusive HDR brachytherapy in tongue carcinoma

Authors	Location	HDR dose/fractionation	Results
Inoue *et al.* [16]	tongue	60 Gy/10#/1 week	4 yr LC – 87%
Leung *et al.* [29]	tongue	55 Gy/10#/6 days	5 yr LC – 94.7%
Yamazaki *et al.* [30]	tongue	48-60 Gy/8-10#/ 6-7 days	5 yr LC – 84%
Kakimoto *et al.* [31]	tongue	54-60 Gy/9-10#/ 5-7 days	5 yr LC – 85.9% OS – 80.3%

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