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GEC-ESTRO/ACROP recommendations

# GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update – Improvement by cross sectional imaging based treatment planning and stepping source technology

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ABSTRACT

The Head and Neck Working Group of the GEC-ESTRO (Groupe Européen de Curiethérapie – European Society for Therapeutic Radiology and Oncology) published in 2009 the consensus recommendations for low-dose rate, pulsed-dose rate and high-dose rate brachytherapy in head & neck cancers. The use of brachytherapy in combination with external beam radiotherapy and/or surgery was also covered as well as the use of brachytherapy in previously irradiated patients. Given the developments in the field, these recommendations needed to be updated to reflect up-to-date knowledge.

The present update does not repeat basic knowledge which was published in the first recommendation but covers in a general part developments in (1) dose and fractionation, (2) aspects of treatment selection for brachytherapy alone versus combined BT + EBRT and (3) quality assurance issues.

Detailed expert committee opinion intends to help the clinical practice in lip-, oral cavity-, oropharynx-, nasopharynx-, and superficial cancers. Different aspects of adjuvant treatment techniques and their results are discussed, as well the possibilities of salvage brachytherapy applications.



Locoregional failure is the predominant pattern of failure in head and neck (H&N) cancer [1] and the majority of local failures are identified in the high-dose areas of modern radiochemotherapy series [2,3]. Hence, local dose intensification is an unmet need in H&N cancer, especially taking into account that large cohort analysis data showed that local control was the most significant variable affecting the development of distant metastasis [1–4].

Brachytherapy (BT) alone or in combination with external beam (EBRT) and chemotherapy leads to local dose escalation over the possibilities of up-to-date EBRT technologies. Major advantages of modern brachytherapy are the use of imaging in BT target and organ of risk definition, the implementation of stepping source technology with the potential for intensity modulation and the developments in medical and physics quality assurance (QA).

The GEC-ESTRO Head & Neck Working Group published the first recommendations in 2009 [4]. In this update the recommended standards of H&N BT by the use of stepping source technology and cross sectional imaging based treatment planning are considered; however, without discussing recommendations regarding the use of imaging technology. Generally, we advice to use MRI for definition of tumor extension and CT for investigating bone involvements. PET could be useful for staging procedures and for differentiation between scar and biologically active tumor tissue as well for information on hypoxic regions.

## General aspects of treatment planning: dose and fractionation

Target definition of the Gross Tumor Volume (GTV) and Clinical Target Volume (CTV) are usually performed by clinical examination aided by imaging and intraoperative findings. In brachytherapy, typically no additional margin is required to ensure that the

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CTV receives the planned dose and therefore, unlike external beam irradiation, CTV and PTV (Planning Target Volume) are considered equivalent. The classical Paris system rules combined with cross sectional imaging offers useful help in preimplant determination of the number of planes, the number of catheters and the spacing depending on the CTV characteristics.

Brachytherapy in the H&N area is usually delivered through fixed applicators (plastic tubes or steel needles) inserted with a margin of 5–10 mm around the CTV. An appropriate implant geometry to the CTV is essential to provide an adequate target coverage and a favorable dose non-uniformity ratio ($V_{100:}$ $V_{150}$ = DNR). The optimal spacing between applicators is $\leqslant$15 mm [5]. Surface mold applications are sometimes useful for superficial tumors of the head and neck region.

Dose planning and dose calculation should be based on 3D studies from a CT or MRI scan. The prescription dose is usually the minimum dose received by the CTV or a CTV surrogate (i.e., the $D_{90}$ > 100, $V_{100}$ > 90%). Dose inhomogeneities need to be minimized following general rules such as those derived from the Paris system [6,7] with additional optimization if needed, mainly by geometrical and graphical methods [8] which is possible in stepping source systems. A cautionary measure is to keep the hyperdose sleeves (200% isodose volumes) as thin as possible and not confluent with other applicator sleeves [6]. DNR should be equal or lower than 0.36 and in IMBT (intensity modulated Brachytherapy) 0.42 [9]. However, in small GTVs (few $cm^3$ and applicator spacing of less than 10 mm) the DNR may be as high as 0.50–0.52. Dose through the skin should be avoided if possible - except when using surface molds or at the skin involving cancers.

Standardized Organ at Risk (OAR) dose–volume constraints in H&N brachytherapy are lacking. It is wise, however, to keep the dose in bone, nerves, vessels and other dose-limiting organs as low as possible provided that the CTV coverage is adequate (i.e., $D_{90}$ is at least 90% of the prescribed dose). The use of lead sheets or plastic spacers is encouraged to reduce the dose to the ipsilateral mandible in oral cavity implants.

The dose administered in H&N brachytherapy depends on the actual indication for therapy and given type of fractionation. Due to lack of large cohort randomized data retrospective series with long term follow-up has to be relied on. Most available outcome data come from the LDR Ir-192-wire era and should be used as a reference when proceeding to modern fractionation schedules of PDR and HDR. The LQ (Linear-Quadratic) model with an $\alpha/\beta$ ratio of 10 Gy and a repair half-time of 1.5 h could be used to calculate iso-effective doses of different fractionation schedules [4]. Recommendations from ICRU report 58 should be used when reporting brachytherapy [10].

When moving from LDR to PDR it must be taken into account that the original PDR schedule with 0.5 Gy/pulse every hour during both day and night was designed to be biologically equivalent to LDR [11]. It has also been postulated that pulsing every second or third hour would be equivalent [12]. Long term clinical outcome data with PDR 24 pulses per day and 12 pulses per day are now available [13–16]. In contrast, when moving from LDR to HDR the total treatment dose has to be reduced depending on the dose per fraction. To be able to deliver the HDR brachytherapy in a short overall time most institutions use 2 fractions per day with a minimum of 6 h interval that is the time required to allow complete repair of sublethal damage. A meta-analysis did not reveal significant differences in outcome compared to LDR, but the data need to be interpreted with caution [17]. Table 1 gives an overview of proposed fractionation schedules for PDR and HDR.

## General aspects of treatment selection: BT alone versus BT + EBRT

### *Brachytherapy alone*

Brachytherapy alone has been nowadays replaced by surgery in the treatment of most T1 and T2 tumours due to advances in surgical and anesthetic procedures that have been proven safe and effective even in frail patients; however, no randomized trial has ever compared surgery versus brachytherapy in primary tumours. In addition, surgery provides a complete pathological documentation of the extent of disease that allows an individualized adjuvant treatment plan for subsequent radiotherapy.

However, brachytherapy alone remains an acceptable mode of treatment in intact T1 and small T2 tumours with low risk of lymph node involvement that meets at least one of the following criteria: 1/Patient decision; 2/Tumor location in areas of functional importance (lip commisure, etc.); 3/Tumor location in areas of cosmetic relevance such as the periorificial zone (eyelids, pinna, ears,.) 4/ Medical contraindication for radical surgery. Ninety percent of the cases described above are locally controlled after LDR/PDR doses of 60–70 Gy with hourly doses in the 0.4–0.7 Gy range [18]. These results underline the equal effectivity of brachytherapy compared to surgery in nodal negative T1-T2 cancers.

Finally, patients with 5/Small tumors of 3 cm or less arising in previously irradiated areas not suitable for surgical salvage are also potential candidates for primary brachytherapy alone with dose and volume adjustments aimed to minimize potential complications derived from cumulative dose. Ten years local control rates of salvage brachytherapy with simultaneous chemotherapy are by 75%.

### *Combined EBRT + brachytherapy*

The combination of external beam irradiation and brachytherapy for H&N cancers follows the same principles applied in other tumor sites treated with combined modality therapy such as advanced cervical cancer. Brachytherapy is used as a boost 1–2 weeks after the completion of EBRT, usually in the form of IMRT (Intensity Modulated Radiation Therapy) or VMAT (Volumetric Arc Therapy). Cisplatin-based chemotherapy is commonly added in the more advanced cases. Attempt should be made to keep the overall treatment time similar to EBRT alone.

**Table 1**
Different PDR and HDR schedules for H&N BT proposed in litterature.

| Brachytherapy schedule | | | Mono (Gy) | Boost (Gy) | Surgery + BT (Gy) | Reference |
|---|---|---|---|---|---|---|
| PDR 0.4 Gy | 24 pulses/d | | 70 | 30 | 50–70 | [14,16,40] |
| PDR 0,8 Gy | 12 pulses/d | | 60 | 30–35 | 50–60 | [29] |
| HDR 2,5 Gy | 2 fx/d | 5d/w | 34–36* | 10–20 | 30–36* | [91,92] |
| HDR 3 Gy | 2 fx/d | 5d/w | – | 18 | 54 | [45,61] |
| HDR 4 Gy | 2 fx/d | 5d/w | 36 | – | 32–40 | [32,70] |
| HDR 5 Gy | 2 fx/d | 5d/w | 45 | – | – | [31] |
| HDR 6 Gy | 2 fx/d | 5d/w | 48 | 21 | – | [43] |

* Depends on the implant inhomogeneity.

Combined EBRT and brachytherapy is an acceptable mode of treatment in 1/intact T1-2 tumors in patients ineligible for surgery as described before but with a substantial risk of lymph node involvement, 2/advanced T3-4 and/or N + tumors that would require surgical resections with functional or cosmetic impact (i.e. cheek, base of tongue, etc.); 3/tumors of different locations eligible for primary radiotherapy in whom a brachytherapy boost outweighs the discomfort of an interventional procedure (i.e., soft palate, tonsil, etc.). In addition, the dosimetric superiority of a brachytherapy boost allows local dose escalation in biologically defined PTV subvolumes, although further studies are needed in this field [19–22]. Local control rates in excess of 80% are commonly reported in different tumor sites treated with a standard combination of 45-50 Gy of EBRT and 15-20 Gy of LDR brachytherapy (or PDR/HDR equivalent). Combined external irradiation and brachytherapy is recommended as the reference treatment if brachytherapy is indicated in oropharyngeal tumors.

## General aspects of quality assurance and physical aspects

### *Implant Check*

Before the first fraction takes place it is advisable to check manually the clearance of the catheter paths using a dummy wire. Too narrow catheter diameters or kinks can be detected in this way. This maneuver also allows checking the resistance to the passage of the source of each individual catheter. Resistance can be anticipated by the position and curvature of the catheters in the 3D image reconstruction. The measured length can be compared against the length of the catheter in the treatment planning system. If differences occur, a closer look is necessary. Sometimes it is necessary to implant catheters in a loop technique. If the loop diameter is close to the minimum allowed diameter of the afterloading unit for such techniques as described in the afterloader specification, care should be taken when treating with these tubes. If treatment is not possible, the kinked catheter can be separated virtually into two parts – if you use an afterloader with free adjustable source path lengths and the loop has enough free distance at both legs for transfer tube connection. That means the treatment plan must be changed, such that the source is entering the kinked catheter from both sides up to the position where the resistance occurs. These lengths must be measured and incorporated into the TPS and afterward the treatment plan updated.

### *Treatment planning*

Catheter reconstruction is an important step in the planning process of head and neck brachytherapy. Catheters must be well visible in the 3D imaging, typically in CT. To enhance the visibility of plastic catheters thin metal wires may help when inserted into the catheters before scanning the patient. A CT slice thickness of 0.2–0.3 cm (in small tumors 0.1 cm) should be adequate to accurately reconstruct each individual catheter. Numbering of catheters in the treatment planning system must reliably reproduce the numbering at the implanted catheters, e.g. using labels fixed at the implant tubes. In case of doubt, individual markers for each catheter can be used in a repeat CT scan.

### *Dose calculation*

The dose calculation in brachytherapy is typically performed using the TG-43 formalism [23]. Nevertheless, this highly standardized dose calculation method does not take into account tissue inhomogeneities or finite patient dimensions. Since a few years model-based dose calculation algorithms became commercially available in brachytherapy [24]. So far it seems that for head and neck HDR techniques the impact of the dose calculation algorithm on dose distributions of the CTV is limited [25].

### *Treatment delivery*

When connecting and disconnecting the catheters to the transfer tubes of the afterloading machine, care must be taken to avoid displacements of the implanted catheters. When a patient is disconnected after a treatment fraction, the implant tubes should be closed with mandrins. This is to prevent kinking of the catheters and to keep the inner part of the catheters clean.

## Primary brachytherapy

### *Lip cancer*

LDR brachytherapy has proven to be an effective treatment option in lip carcinoma with a 5-year failure rate well below 10% and good functional and cosmetic results [26]. Complications have been described in 2–10% of the patients with soft tissue or bone necrosis [4]. Most of the applications are interstitial, however, small series are published with the use customized molds [27]. Up-to-date interstitial implant geometry follows the classic rules of the LDR implants, using parallel needles or plastic tubes with template fixation. The CTV is the visible or palpable GTV with a safety margin of 5–10 mm. LDR and HDR brachytherapy have produced similar results in three intramural studies with local control rates in the 90–95% range and similar toxicity [28–30]. Guinot et al. compared 99 LDR cases and 104 HDR cases with similar local control (95%) but fewer complications using HDR and no case of bone or soft tissue necrosis in the last group [31]. PDR is effective with local control of 94% [32] Most cases are treated with brachytherapy alone although elective cervical treatment should be considered in lip tumors larger than 2 cm or with skin or commissure involvement [33].

### *Oral cavity cancer*

Most frequent sites are floor of mouth, oral tongue and oral mucosa. Implant technique and indication may differ according to the given anatomic situation. Double planar straight tube technique is the most common technique [34]. If this technique is used, additional buttons or a non-looping loop [35,36] are required to avoid underdosage of the mucosa of the dorsum of tongue. Spacers are mandatory to reduce the dose to the mandible as well as to the mucosa of the palate. Combined modality therapy with 15–30 Gy of brachytherapy as a boost after 46–50 Gy of EBRT is the most common indication in advanced cases. Local control appears to increase with the given proportion of brachytherapy dose [37]. In the monotherapy situation, a small randomized trial of 59 patients with cancer of oral tongue performed in Japan compared LDR 70 Gy over 4–9 days with HDR 60 Gy in 10 fractions. The 5-year local control rates were comparable between HDR (87%) and LDR (84%) brachytherapy [38]. Complications of the technique include soft tissue necrosis and bone necrosis in 10–30% of the implants using HDR. Meta-analysis of 6 trials constituting 1 randomized trial and 5 controlled trials with 607 patients (LDR = 442, HDR = 160) revealed no statistically significant differences between LDR and HDR in terms of local recurrence, overall mortality and grade 3/4 complications [17]. PDR brachytherapy has also been reported to result in outcomes comparable to that of LDR [16]. In floor of mouth tumors, Inoue et al. reported a 5-year local control of 94% in a small series of patients treated with HDR [39]. PDR brachytherapy has been used in floor of mouth cancers with doses similar to the mobile tongue and excellent outcomes [40]. T1–T2 tumors of the hard palate can be treated with surface mold

brachytherapy. Customized carrier prosthesis with tubes mounted over it could be prepared for HDR brachytherapy. Dose of 60–65 Gy LDR equivalent could be given with 3–4 Gy/fraction. There is lack of outcome data for surface mold brachytherapy using HDR.

*Oropharynx cancer*

Interstitial brachytherapy for oropharyngeal tumors (base of tongue, valleculla, tonsil, soft palate and uvula) has resulted in excellent local control rates of 80–90% using low dose rate brachytherapy techniques [4]. Due to high propensity for lymph node metastases brachytherapy is combined with EBRT. One of the additional advantages of brachytherapy for oropharyngeal tumors is a reduction of xerostomia over IMRT and sparing of dysphagia aspiration related structures (DARS). With combined IMRT and BT approach there is a reduction of grade $\geqslant 2$ xerostomia and dysphagia which has been reported in only 11% and 8% respectively. Oropharyngeal implants are technically demanding and there are several requirements that need to be met: 1/Adequate mouth opening under nasotracheal intubation; 2/Small residual lesions after EBRT that can be safely encompassed within the prescription isodose; 3/Airway protection with temporary tracheostomy, however, it should be discussed case by case depending on the risk assessment of severe dyspnea; 4/Wider loops or non-looping techniques if stepping sources are used. There are a few series of brachytherapy for oropharyngeal tumors using stepping source of PDR or HDR. One of the largest series from the Netherlands reported local control rates of 94% and overall survival of 72% at 5 yrs using HDR brachytherapy as a boost [41]. In other series the local control rates as high as 80–85% have been reported with HDR brachytherapy. Complications of the treatment include soft tissue necrosis which is observed in 4.5–29% patients. Osteoradionecrosis is observed in 1% of the cases [42–45].

*Nasopharyngeal cancer*

Intracavitary brachytherapy for nasopharyngeal tumors has resulted in excellent results in early cases in which the local tumor extension can be adequately encompassed within the prescription isodose [4,18]. The Rotterdam group reported significant differences in local control between patients treated with or without a brachytherapy boost in the pooled analysis for T1–T2 N+ cases, thus confirming the results of other investigators with early local disease [46,47]. Larger tumors are nowadays better suited with high-precision external techniques although the development of endoscopically-guided intracavitary-interstitial devices may extend the brachytherapy indications for this location [48,49].

*Superficial cancer*

Shallow (less than 0.5 cm thick) head and neck tumors arising in certain sites such as scalp, face, pinna, lip, buccal mucosa, maxillary antrum, hard palate, oral cavity external auditory canal, and the orbital cavity after exenteration can be treated with brachytherapy with surface molds or prosthesis. Mold therapy is excellent for the treatment of superficial carcinomas because it allows the planning of an adequate dose distribution before treatment and provides highly reproducible irradiation [50,51]. The dose is prescribed at a certain depth like 5 mm or at the skin surface in between the catheters. The treatment depth may be modulated by optimization in relation to the tissue thickness and the skull bone [52,53]. A total HDR dose equivalent to about 60 Gy LDR (prescribed at 0.5 cm depth) is recommended. The actual HDR dose per fraction and number of fractions can be varied to suit individual situations (including site and treatment volume). HDR-BT can also be used as a boost to 45–50 Gy EBRT, in which cases the HDR doses are appropriately reduced to LDR equivalent doses of 15–30 Gy [54–60].

## Adjuvant brachytherapy

Some patients who are treated primarily with surgery and present high risk features of local failure (i.e., positive margins, etc.) require adjuvant irradiation. Brachytherapy alone is an ideal adjunct in this setting provided that the following criteria are met: 1/the high-risk area can be precisely defined (i.e., clip placement during surgery) and is accessible to implantation; 2/external irradiation is not required (i.e., node dissection is negative, etc.) or is contraindicated (i.e., prior irradiation), and 3/Repeat surgery to obtain wider margins is not an option due to functional or cosmetic concerns. In some cases, adjuvant brachytherapy can be combined with external irradiation for dose intensification in high-risk areas with the added advantage of shortening the overall treatment time and decreasing the external component.

Adjuvant brachytherapy has been traditionally given postoperatively (PoB) 1 to 2 months after the surgical procedure. Limitations of this procedure are the need for a second interventional procedure and the lack of precise definition of the high risk area. Perioperative (PeB) and intraoperative brachytherapy (IoB) are investigational treatment modalities that overcome the limitations of delayed target definition with the placement of the intraoperative applicator or the afterloading catheters is intraoperatively. IoB treatment is HDR-based and is completed in less than 2 h. PeB and PoB treatments can be delivered with LDR, PDR or HDR brachytherapy. Treatment duration for PeB and PoB is typically 2–5 days.

In PoB, the different LDR or PDR regimens reported use 45–60 Gy when brachytherapy is used as the only adjuvant to 22–29 Gy when brachytherapy is coupled with 47–60 Gy of EBRT [16,61–65]. Customary IoB doses are 12–15 Gy prescribed at a depth of 5 mm from the surface of the applicator [66,67]. The experience of the combination of IoB and EBRT is very limited. In PeB, the different treatment regimens used vary from 30 to 40 Gy in 8–10 b.i.d. treatments when HDR is used as the sole treatment modality [68–70] to 16–24 Gy in 4–6 b.i.d. treatments when HDR brachytherapy is combined with 30–45 Gy of external irradiation. In PeB studies with LDR brachytherapy as the sole adjuvant treatment, typical radiation doses are 60 Gy delivered over 4–5 days [71,72].

PoB series report an overall rate of complications grade 3 or greater in 2.8–30.5% of the cases with a median of approximately 14%. Namely, grade 3 bone damage and grade 3 soft tissue necrosis are consistently reported in 3–9% and 3–14% of the cases, respectively [16,63,65]. The assessment of toxicity in IoB and PeB series is more difficult to undertake since surgical and radiation-derived complications sometimes overlap. In addition, an overwhelming majority of PeB and IoB patients are previously irradiated cases. The antecedent of prior irradiation is the strongest risk factor for severe toxicity [70]. Overall, grade 3 or greater complications have been reported in 15–69% of the cases with a median of approximately 21%. Namely, grade 3 bone damage and grade 3 soft tissue necroses have been consistently reported in 4.5–15.4% and 5–11% of the cases, respectively [16,63,65]. Nerve damage has been observed in 2–5% of the cases due to the antecedent of prior irradiation [68–72] and it is related to re-irradiation.

PoB series report 5-year locoregional control rates in the 72–93% range [16,63,65] with the upper figures corresponding to early cases treated with PoB alone and the lower figures to advanced cases treated with a combination of EBRT and PoB. Most patients treated with PoB are primary cases. PeB and IoB series report 2 and 5-year locoregional control rates of 60–70% and 40–60%, respectively. Most patients treated with either PeB or IoB are recur-

rent previously irradiated cases treated with either IoB or PeB alone. Additional low-dose EBRT was given to one-quarter to one-third of the cases. Margin status and tumor bulk are the main predictors of locoregional control in all three-treatment modalities.

PoB series report 5-year overall survival rates in the 50–75% range. The upper figures correspond to early primaries and the lower figures to more advanced cases. PeB and IoB series report 2 and 5-year overall survival rates of 60–65% and 23–50%, respectively [63,68,72].

## Salvage brachytherapy

Brachytherapy can be used in this setting in two different scenarios: 1/Previously Irradiated H&N cancer, or 2/Primary tumors arising in a previously irradiated field. Although salvage external beam radiation therapy (re-EBRT) is technically possible, it is rarely attempted because of its low effectiveness and associated high complication rates [73]. In resectable tumors, surgery should be considered first but the percentage of inadequate resections due to positive margins is extremely high and adjuvant re-irradiation in the form of brachytherapy is an acceptable treatment option [74]. In patients ineligible for surgical salvage, brachytherapy is an acceptable option provided that the coverage of the CTV is adequate and there is not advanced bone invasion, fistula or limited life expectancy. Brachytherapy in previously full course irradiated regions needs to follow the same principles as primary brachytherapy with more strict dose and volume constraints [75,76].

The observed local control rates of salvage LDR/PDR/HDR brachytherapy vary widely – between 16 and 86% after 2- to 5-years [77–90,97–98]. Additionally, interstitial brachytherapy can play an important role in the treatment of lymph node recurrences of head and neck cancer. Using image-guided interstitial HDR-brachytherapy for re-irradiation of recurrent lymph node metastases of head and neck cancer, local control probabilities on the order of approximately 60–70% have been published [88]. Finally, Strege [91,92], Mazeron [93], Peiffert [94,95], Pommier [96] and Strnad [97,98] reported about local long-term control rates up to 80% and with severe toxicity (bone or soft tissue necrosis) under 4%. Small cohort of a single institution indicate the usefulness of combining debulking surgery with HDR in combination with chemotherapy [99].

## Conclusion

Modern BT is playing an important and successful role in the multidisciplinary treatment of head and neck cancer. It can be used as a sole treatment for several T1/T2 cancers and it is also effective in complementary to EBRT as a local dose escalation method as well as combined with surgery as a small volume radiation with high geographic accuracy. In technically feasible cases BT offers a valuable treatment choice also for salvage treatments.

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## Conflict of interest statement

The authors declare that they have no competing interests.

None of the authors has any financial and personal relationships with other people or organisations that could inappropriately influence (bias) of this work.

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