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American Brachytherapy Society Task Group Report: Combined external beam irradiation and interstitial brachytherapy for base of tongue tumors and other head and neck sites in the era of new technologies

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ABSTRACT Irradiation plays an important role in the treatment of cancers of the head and neck providing a high locoregional tumor control and preservation of organ functions. External beam irradiation (EBI) results in unnecessary radiation exposure of the surrounding normal tissues increasing the incidence of side effects (xerostomy, osteoradionecrosis, and so forth). Brachytherapy (BT) seems to be the best choice for dose escalation over a short treatment period and for minimizing radiation-related normal tissue damage due to the rapid dose falloff around the source. Low-dose-rate BT is being increasingly replaced by pulsed-dose-rate and high-dose-rate BT because the stepping source technology offers the advantage of optimizing dose distribution by varying dwell times. Pulsed-dose and high-dose rates appear to yield local control and complication rates equivalent to those of low-dose rate. BT may be applied alone; but in case of high risk of nodal metastases, it is used together with EBI. This review presents the results and the indications of combined BT and EBI in carcinoma of the base of tongue and other sites of the head and neck region, as well as the role BT plays among other—normal tissue protecting—modern radiotherapy modalities (intensity-modulated radiotherapy, stereotactic radiotherapy) applied in these localizations.

Keywords: Brachytherapy; External beam; Tongue

Introduction

Irradiation, alone or combined with chemotherapy (ChT) or biological therapy, as an organ-preserving modality plays an important role in the treatment of cancers of the head and neck (H&N) providing—besides retaining speech and swallow functions practically completely as well as yielding good cosmetic results—a high locoregional tumor control (LRTC). However, delivering maximal doses with external beam irradiation (EBI) to the target volume for better local control (LC) results in unnecessary radiation exposure of the surrounding critical organs (salivary glands, mandible, masticatory muscles, and so forth) thereby increasing the incidence of side effects (xerostomy, osteoradionecrosis [ORN], fibrosis, trismus, and so forth). Intensity-modulated radiotherapy (IMRT) can decrease toxicity, but brachytherapy (BT)—although it is an invasive method requiring special skills and interdisciplinary co-operation with the (H&N) surgeon—seems to be the best choice for dose escalation over a short treatment period and for minimizing radiation-related normal tissue damage,

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due to the rapid dose falloff around the source (1, 2). Low-dose-rate (LDR) BT was the gold standard until the end of the 20th century. Extensive experience with LDR BT has been described in the literature (1–3). Nowadays in several institutions, HDR and pulsed-dose-rate (PDR) BT have replaced LDR BT, because these stepping source technologies offer the advantage of optimizing dose distribution by varying dwell times (2, 3). Although the application of HDR BT is growing worldwide, it is still not widely used because of lack of experience and biological concerns. The potential radiobiological "disadvantage" of HDR can be compensated with twice-a-day (a minimum interval of 6 hours) fractionation schedule and limited fraction doses ≤ 6 Gy (3–5). For these reasons, the Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (ESTRO) recommend using fraction dose <3–4 Gy and the American Brachytherapy Society (ABS) ≤6 Gy per fraction (3, 4).

On the basis of relevant results from the literature, HDR appears to yield LC and complication rates equivalent to those of LDR (2, 6–10).

BT may be applied alone or combined with surgery in early stage lesions of the oral cavity (OC), where the risk of regional metastases is low. In advanced cases or if there is a high risk of nodal metastases, it is used together with EBI. BT is also a reasonable treatment choice in previously irradiated recurrent cancer, due to tumor extension precluding complete resection with clear surgical margins. In the literature, the most frequently applied isotopes are ^{226}Ra, ^{125}I, ^{222}Rn, ^{131}Cs, ^{198}Au, and ^{192}Ir. The latter is nowadays the most commonly used worldwide.

This review presents the results and indications of combined EBI and BT in carcinoma of the base of tongue (BOT) and other sites of the H&N region and deals with the role of BT among other radiotherapy modalities (IMRT, stereotactic radiotherapy [SRT]) in these localizations.

Methods

For this review, the literature search was performed in MEDLINE (via Pubmed) and limited to articles dealing with BOT, OC, oropharynx (OP), nasopharynx (NP) cancer, and perioperative and intraoperative cases treated with the combination of EBI and BT. Relevant articles with higher number of patients and with appropriate statistical analyses were assessed, but for BOT, we applied a more detailed analysis. Using this method, we selected 83 articles.

EBI + BT in BOT cancer

In the treatment of BOT tumors, the "organ-preserving" modalities have become more and more important, because unlike surgery, which often results in significant morbidity and poor quality of life (QOL) due to impairment of speech and swallowing, they provide a practically complete retaining of functions as well as good cosmetic results and a high LRTC. In a retrospective comparison of outcomes of surgery and RT from different medical centers in the United States, it was found that severe complications occurred in 32% vs. 3.8% in those who underwent upfront surgery vs. radiation (11). So RT with/or without ChT is the most important tool of this kind of treatment (12–24). Local tumor control can be increased without unnecessary radiation to the surrounding normal tissues by local dose escalation using interstitial BT (IBT) boost after EBI (13–19, 25–36). EBI is an essential component in the treatment of the OP because of the propensity of the disease to spread to the lymphatics (37).

In the OP region, the BOT is the most frequent site for BT. LDR BT has been applied for a long time in the treatment of BOT tumors with a good effectivity (13–19, 25–33), but only a few analyses can be found in the literature on the application and efficacy of HDR BT (7, 33–35).

Earlier, it was more common to treat BOT cancer exclusively with EBI. Five-year LC has been reported in the range of 28–70%. Based on tumor (T) size, LC was 72–100% for T1, 54–89% for T2, 32–67% for T3, and 11–20% for T4. Five-year overall survival (OS) was between 22% and 44% (27, 31, 38–44). As to the incidence of grade 4 toxicities, soft-tissue necrosis (STN) and ORN occurred in 0–20% and 0–16%, respectively (26, 44–46).

Authors using LDR BT boost after EBI reported an improved 5-year LC (Table 1) of 64–89%. Five-year OS (Table 1) was reported in the range of 26% and 87% (13–16, 18, 19, 25–33). The time interval between the end of the EBI and the start of the LDR boost varied between 1 and 69 (mean 21) days. As severe (grade 4) side effect, STN occurred in 2.5–27% and ORN in 0–6% (13–16, 18, 19, 25–34, 47).

There are only few data available about the role of HDR BT boost in the treatment of BOT tumors (Table 1). van de Pol *et al.* (33) treated 30 patients with EBI and LDR, PDR, or HDR BT boost. LDR and HDR (24–35 Gy) treatment was carried out in 16 and 5 cases, respectively, while PDR (20–28 Gy) in 9 cases. Cano *et al.* (34) presented 88 patients with LDR (n = 11) or HDR (n = 77) boost. Local recurrence rate was 18.9%. In these studies, LDR and HDR results were not analyzed separately. Results are summarized in Table 1.

In the analyses of Takacsi-Nagy *et al.* (7) with HDR boost, the dose of EBI was 60 Gy and the BT dose was 12–30 Gy. Implantations for BT were carried out 2–6 (mean 3) weeks after completing EBI. The 5-year actuarial LC by T-status was100% for T1, 75% for T2, 61% for T3, and 52% for T4, whereas in the LDR series on average, it was 85–100% for T1, 50–100% for T2, and 46–100% for T3-T4 (13–16, 18, 19, 25–33).

Johansson *et al.* (36) published results with PDR BT. EBI dose was 1.7 Gy, twice daily to 40.8 Gy or 46–50 Gy used with conventional fractionation. BT dose was 30 or 35 Gy. The median time interval between the end of the EBI and

Table 1
Results of BT for base of tongue cancer

Author	*n* and T status	T4 (%)	BT and EBI dose (Gy)	Dose rate	LC (y)	OS (y)	Toxicity
Lusinchi *et al.* (13)	108 T1:18,T2:39,T3:51	0	22–88 +45 EBI	LDR (^{192}Ir)	64% (5 y)	26% (5 y)	25% STN
Pernot *et al.* (25)	72 T1:14,T2:27,T3:25,T4:6	8	20–30 +40–50 EBI	LDR (^{192}Ir)	72% (5 y)	44% (5 y)	NR
Puthawala *et al.* (14)	70 T1:2,T2:16,T3:40,T4:12	17	20–25 (T1-2) 30–40 (T3-4) +45–50 EBI	LDR (^{192}Ir)	83% (5 y)	35% (5 y)	11.4% STN, 3% ORN
Harrison *et al.* (15)	68 T1:17, T2:31, T3:18, T4:2	3	20–30 +45–54 EBI	LDR (^{192}Ir)	89% (5 y)	87% (5 y)	13% STN, 3% ORN
Crook *et al.* (16)	48 T1:13, T2:35	0	60–70 alone or 20–35 + 30–60 EBI	LDR (^{192}Ir)	75% (5 y)	50% (5 y)	30% STN, 6% ORN
Housset *et al.* (26)	29 T1:6, T2:23	0	30–35 +45 EBI	LDR (^{192}Ir)	79% (5 y)	52% (5 y)	7% STN, 3% ORN
Demanes *et al.* (27)	25 T1-4	16	19.2–36.9 +50–62.5 EBI	LDR (^{192}Ir)	NR	36% (5 y)	NR
Robertson *et al.* (28)	20 T1:3, T2:10, T3:6, T4:1	5	25.5–30 +50–54 EBI	LDR (^{192}Ir)	NR	38% (5 y)	NR
Horwitz *et al.* (17)	19 T1:4, T2:7, T3:5, T4:3	16	20–32 +50.4–66.6 ±ChT	LDR (^{125}I)	83% (5 y)	64% (5 y)	5% STN, 10% ORN
Goffinet *et al.* (18)	14 T1:3, T2:4, T3:5, T4:2	14	20–25 +50–55 EBI	LDR (^{192}Ir)	86% (3 y)	70% (5 y)	14% STN, 7% ORN
Gibbs *et al.* (19)	41 T1:7, T2:14, T3:10, T4:10	24	20–34 48.9–68	LDR (^{192}Ir)	82% (5 y)	66% (5 y)	7% STN, 5% ORN
Cano *et al.* (30)	18 T1:1, T2:3, T3:4, T4:10	56	12–34 +50–75 ±ChT	LDR (^{192}Ir)	89% (5 y)	53% (5 y)	5% STN
Barrett *et al.* (31)	20 T1:2, T2:11, T3:4, T4:3	15	20–30	LDR (^{192}Ir)	87% (5 y)	33% (5 y)	NR
Karakoyun-Celik *et al.* (32)	40 T1:8, T2:11, T3:16, T4:5	13	10–35 +50–72 EBI ±ChT	LDR (^{192}Ir)	78% (5 y)	62% (5 y)	5% ORN
van de Pol *et al.* (33)	30 T3:10, T4:20	67	24–35 (LDR) 24–35/3–4/fr. (HDR) 20–28 (PDR) +46 EBI	LDR/HDR/PDR (^{192}Ir)	65% (5 y)	37% (5 y)	NR
Cano *et al.* (34)	88 T1:7, T2:30, T3:22, T4:29	33	18–29.5/3–3.5/fr. (HDR) 18–29.5 (LDR) +50.4–70.2 EBI ± ChT	HDR/LDR (^{192}Ir)	NR	81% (3 y)	4.5% STN
Takácsi-Nagy *et al.* (7)	60 T1:2, T2:5, T3:17, T4:36	60	12–30 (3–4/fr.) +60 EBI ±ChT	HDR (^{192}Ir)	57% (5 y)	47% (5 y)	12% STN, 2% ORN
Johansson *et al.* (36)	83 T1:8, T2:41, T3:14, T4:20	24	35 +1.7 (bid) 40.8 EBI ±ChT	PDR (^{192}Ir)	89% (5 y)	65% (5 y)	6% STN, 7% ORN

n = number of patients; BT = brachytherapy; EBI = external beam irradiation; T = tumor; LC = local control; OS = overall survival; y = years; LDR = low-dose rate; PDR = pulsed-dose rate; HDR = high-dose rate; fr. = fraction; ChT = chemotherapy; NR = not reported; STN = soft-tissue necrosis; ORN = osteoradionecrosis; bid = twice-a-day.

PDR boost was 17 (8–31) days. LC according to T1-4 status was 100%, 98%, 93%, and 65%, respectively.

The mean rate of T4 tumors in these BOT studies was 24% (range, 0–67%) (13–16, 18, 19, 25–34, 36). Only in the studies of Cano *et al.* (30), Takácsi-Nagy *et al.* (7), and van de Pol *et al.* (33) was the rate of T4 tumors higher than 50% (56%, 60%, and 67%).

Barrett *et al.* (31) compared retrospectively surgical resection and postoperative RT, definitive EBI, and EBI with LDR BT boost in the curative treatment of BOT (T1-4) tumors. Five-year LC and OS were 74% and 44%, 28% and 24%, 88% and 33%, respectively.

OC cancer

Interstitial or mold BT (gingiva, hard palate, and so forth) is indicated in lip and OC carcinomas as an exclusive treatment for tumors with size < 30–40 mm without bone infiltration and lymph node metastases. BT as a boost after EBI is indicated for tumors not amenable to surgery and if their size is 30–40 mm at the time of implantation. Contraindications of BT include >1-cm invasiveness in width to the gingiva and bone infiltration (3, 4, 48).

The need for EBI in T1-2 tongue tumors depends on the depth of tumor invasion. The risk of occult nodal metastases increases with the thickness of the tumor (49, 50). In tongue cancer, Fukano *et al.* (50) found that the incidence of cervical metastasis increased markedly when the invasion depth was over 5 mm. Subclinical lymph node metastasis of 5.9% was found in the tumors with less than 5 mm of depth, whereas it was 64.7% when tumor depth exceeded 5 mm. So, elective neck therapy (surgery or irradiation) is strongly indicated for tumors exceeding 5-mm invasion (50). Matsumoto *et al.* (51) treated patients with a median dose of 20 Gy EBI, including the primary tumor site and upper jugular lymph nodes, before BT. Thirty-seven patients received concurrent ChT. Most cervical lymph node metastases occurred within the EBI therapy field, which implied that the EBI dose of 20–30 Gy was insufficient to prevent late cervical lymph node metastases. In a study of Mazeron *et al.* (52), 166 T1-2N0-3 patients with mobile tongue cancer (8% had node positive status) were treated with BT. For N0 patients, neck management consisted of surveillance (n = 78) or elective neck dissection followed by EBI in pathologically positive nodes (n = 72) or RT alone (n = 3). Clinically positive nodes (13 patients) were managed by either neck dissection followed by EBI (n = 10) or RT alone (n = 3). Regional control was 79% for N0 patients, improving to 88% after surgical salvage, and 9 of 13 for N1-3 patients.

Vedasoundaram *et al.* (53) published results on BT of the buccal mucosa. In their opinion, HDR IBT used either as a primary treatment modality or as a boost in buccal mucosal cancers provides results comparable to that of surgery with the advantages of organ preservation along with better cosmetic and functional outcomes. In the largest multicentric study done by the Groupe Européen de Curiethérapie, 748 patients were treated for primary buccal tumor with BT alone (31%), combination of EBI + BT (11%), EBI alone (36%), and surgery often followed by RT (22%). For the various treatments, the local failure rate was: 19% for BT alone, 35% for EBI + BT as well as for EBI, and 22% for surgery ± EBI (54).

Representative outcome details of oral tongue, bucca, and floor of mouth EBI ± BT are presented in Tables 2 and 3.

Several studies have emphasized the superiority of IBT in LC compared with EBI alone. In the early 1980s, Mendenhall *et al.* (59) published a retrospective analysis of 147 patients with squamous cell carcinoma of the oral tongue and floor of the mouth who were treated with radical RT. There was an increase in the LC rate of oral tongue cancer

Table 2
Results of BT for oral tongue cancer

Author	n and T status (% of patients with EBI)	BT and EBI dose (Gy)	Dose rate	LC (y)	OS (y)	Toxicity
Matsumoto *et al.* (51)	67 (52%) T1:24 T2:43	10 × 5 or median 20 EBI +10 × 5 ± ChT	HDR (^{192}Ir)	94% (5 y)	88.7% (5 y)	NR
Yamazaki *et al.* (55)	21 (38%) T1:2 T2:14 T3:5	70 (LDR) 10 × 6 (HDR) ±median 30 EBI	LDR (^{226}Ra ^{198}Au, ^{192}Ir)/ HDR (^{192}Ir)	91% (5 y)	83% (2 y)	10% N
Pernot *et al.* (25)	565 (57%) T1:159 T2:239 T3:158 T4:9	70–75 ±40–50 EBI	LDR (^{192}Ir)	67% (5 y)	47% (5 y)	4.2% G3–4
Guinot *et al.* (56)	50 (66%) T1-2:42, T3:8	11 × 4 or 50 EBI + 6 × 3	HDR (^{192}Ir)	79% (5 y)	70% (5 y)	16% STN and 4% ORN

n = number of patients; T = tumor; BT = brachytherapy; EBI = external beam irradiation; LC = local control; OS = overall survival; y = years; LDR = low-dose rate; HDR = high-dose rate; ChT = chemotherapy; NR = not reported; N = necrosis; G = grade; STN = soft-tissue necrosis; ORN = osteoradionecrosis.

Table 3
Results of BT for cancer of the floor of mouth and bucca

Author (localization)	*n* and T status or stage (% of patients with EBI)	BT and EBI dose (Gy)	Dose rate	LC (y)	OS (y)	Toxicity
Floor of mouth						
Pernot *et al.* (25)	207 (51%) T1-3	70–75 ±EBI	LDR (^{192}Ir)	73% (5 y)	49% (5 y)	4.2% G3–4
Inoue *et al.* (57)	57 (63%) T1:26 T2:30 T3:1	8–10 × 6±EBI 65–85 ±30–40 EBI ±ChT	HDR (^{192}Ir) LDR (^{198}Au)	HDR:94% (5 y) LDR:72% (5 y)	NR NR	38% (HDR) 32% (LDR) STN and/or ORN
Bucca						
Tayier *et al.* (58)	133 (44%) I–II	70 ± EBI	LDR (^{198}Au)	87.2 (5 y)	NR	6% ORN
Vedasoundaram *et al.* (53)	33 (85%) T1:5 T2:16 T3:12	11 × 3.5 or 50 EBI + 6 × 3.5 ±ChT	HDR (^{192}Ir)	88.2% (2 y)	NR	3% STN

n = number of patients; T = tumor; BT = brachytherapy; EBI = external beam irradiation; LC = local control; OS = overall survival; y = years; LDR = low dose rate; HDR = high dose rate; ChT = chemotherapy; NR = not reported; G = grade; STN = soft-tissue necrosis; ORN = osteoradionecrosis.

with treatment by radium alone or radium plus <3000 rad of EBI compared with radium plus ≥3000 rad of EBI ($p = 0.02$). Pernot *et al.* (60) in a retrospective comparative study with oral tongue disease proved that applying BT alone ($n = 70$), the outcome was better than combined with EBI ($n = 77$) in T2N0 carcinomas. Five-year LC was 89.8 vs. 50.6%, respectively. The LRTC was also better. The rate of grade 2–3 complications was 11 vs. 10%, in the two groups. Wendt *et al.* (61) treating T1-2N0 tumors with a combination of EBI and BT found a 2-year LC rate of 92% for patients treated with EBI to doses of <40 Gy combined with a moderately high dose of BT compared with 65% for patients who received EBI to doses of ≥40 Gy with lower BT doses ($p = 0.01$). In Japan, Ichimiya *et al.* (62) analyzed the medical records of 133 patients with stage I tongue cancer and concluded that the addition of IBT significantly improves LC after definitive RT (with IBT vs. without it the 5-year LC rate was 89.9% and 68.4%, respectively [$p = 0.003$]). These data provided the rationale to perform IBT in oral cancer patients. Marsiglia *et al.* (63) found that ORN occurred more frequently in patients with poor dental status and in those treated without dental protection during implantation ($p < 0.001$).

EBI + BT in OP cancer other than BOT

In OP cancers, the risk of nodal metastases is high so the combination of BT with EBI is necessary, and interstitial RT is applied as a boost. The tonsillar region, faucial arch, and soft palate can also be treated with BT. In this region, organ-preserving modalities are especially important (speech, swallowing, and so forth). Before the IMRT era, the role of BT was more significant with regard to salivary impairment.

Levendag *et al.* (64) compared EBI + BT and surgery + postoperative EBI in tonsillar fossa and/or soft palate tumors. The LC rates at 5 years after BT vs. surgery were 88% vs. 88%, and OS was 67% vs. 57%. Mazeron *et al.* (65) treated T1 and T2 tonsillar region, soft palate and uvula tumors ($n = 165$) with definitive RT by exclusive Iridium implant or by a combination of EBI and BT. Overall, 5-year survival was 21%, 50.5%, and 60%, while 5-year LC was 58%, 100%, and 91%, respectively ($p < 0.001$). Five-year necrosis rate was 4.5%, 20.5%, and 18%, respectively. Pernot *et al.* (66) in a study of 361 patients with velotonsillar carcinoma proved that tumors with extension to the mobile tongue or the base have a poor prognosis ($p < 0.002$). The recurrence rate was smaller if the total duration of the treatment was <55 days and the number of days between EBI and BT was <20. Similar results were obtained in a retrospective analysis of Hoffstetter at al. (67). In this material, 370 cases of soft palate and tonsillar carcinomas were treated with EBI and BT. The median duration of the total treatment was 57 days. The rate of LC at 5 years was 88% when the treatment time was 7 weeks and 74% when it was 9 weeks ($p = 0.001$). The rate of OS at 5 years was 63 and 44%, respectively ($p < 0.0001$). At 5 years, the rate of LC and OS was 85% and 59% for the group in which the interval between EBI and BT was less than 3 weeks, and 73% ($p = 0.01$) and 38% ($p < 0.001$) when the delay was longer. Pernot *et al.* (66) found that more severe complications (grade 2–3) seemed to occur at dose rates higher than 0.6 Gy/h and total doses higher than 80 Gy. In T1-2 BOT cancers, Crook *et al.* (16) observed a dose response effect with LC of 79% with a combined dose ≥ 75 Gy but only 50% for ≤ 70 Gy.

Representative outcome details for soft palate, uvula, faucial arch, and tonsil EBI ± BT are presented in Table 4.

EBI + BT in NP cancer

RT is the mainstay of treatment, but irradiation alone has a cumulative incidence of persistent local disease of up to 13% (71). The lack of LC, which is related to the total dose

Table 4
Results of BT for soft palate, uvula, faucial arch, and tonsil tumor

Author (localization)	*n* and T status	BT and EBI dose (Gy)	Dose rate	LC (y)	OS (y)	Toxicity
Mazeron *et al.* (65) (soft palate, uvula)	165 (64% BT + EBI) T1:58 T2:107	10–51 +45 EBI	LDR (^{192}Ir)	83% (5 y)	46% (5 y)	18% STN
Behar *et al.* (68) (tonsil, soft palate)	37 T1-2:25 T3-4:12	20–40 +40–66 EBI	LDR (^{192}Ir)	75% (5 y)	64% (5 y)	2.7%–2.7% STN and ORN
Pernot *et al.* (66) (velotonsillar area)	361 T1:90 T2:141 T3:119 T4 = 2 (Tx = 9)	20–30 +50 EBI	LDR (^{192}Ir)	80% (5 y)	53% (5 y)	NR
Levendag *et al.* (69) (tonsil, soft palate)	38 T1 = 5 T2 = 22 T3 = 10 T4 = 1	15–27 (3–5/fr.) HDR or 20–28 PDR +46–50 EBI	HDR/PDR (^{192}Ir)	87% (5 y)	60% (5 y)	5% STN
Nose *et al.* (70) (soft palate, faucial arch, base of tongue)	83 T1 = 7 T2 = 47 T3 = 24 T4 = 5	6 × 3.5 +46 EBI or 8 × 6	HDR (^{192}Ir)	84% (5 y)	64% (5 y)	29% STN

n = number of patients; T = tumor; BT = brachytherapy; EBI = external beam irradiation; LC = local control; OS = overall survival; y = years; fr. = fraction; LDR = low-dose rate; PDR = pulsed-dose rate; HDR = high-dose rate; NR = not reported; STN = soft-tissue necrosis; ORN = osteoradionecrosis.

of radiation given through EBI alone or combined with BT, is an independent prognostic factor for the development of distant metastases (72).

Generally, T1-2 disease localized to the mucosa or submucosa—not involving the bone, not invading the infratemporal space and not extending into other regions of H&N—is amenable to BT boost. The depth of the target volume should not exceed 10 mm (3, 73). For BT of the NP cancer generally an intracavitary BT (ICBT) applicator is used. Deep-seated carcinoma can be treated with interstitial implantation (74). The advantage of ICBT is that the applicator can be inserted under local anesthesia.

Several authors have reported improvement in outcomes with dose-escalation using BT in conjunction with the standard EBI (Table 5). Wang *et al.* (82) reported—analyzing the results of 146 patients—that EBI (60–64 Gy) plus ICBT boost with ^{131}Cs (10–15 Gy) made a 39% (93% vs. 54%) 5-year LC benefit for T1 NP residual lesion (compared with EBI alone). For the T1-2 lesions, the corresponding LC rates were 90% and 59%, for T3 lesions 100 and 64% with or without BT, respectively. Some authors found that the optimal RT dose to the NP area in early stage cancer may be within 72.5–75 Gy and doses of more than 75 Gy did not have significant LC or survival advantage (78, 82). Similar results were reported by Teo *et al.* (75) in a retrospective review of 509 patients, when additional HDR ICBT was used (n = 163) after EBI. The 5-year actuarial rates of local failure were 5.4% vs. 10.3%, with or without BT. Leung *et al.* (80) reported on (n = 257) significantly better results with BT than without BT. Five-year actuarial local failure-free survival, regional failure-free survival, distant metastasis-free survival, progression-free survival, cancer-specific survival (CSS), and OS rates for the BT group, and the control group were 95.8% and 88.3% (p = 0.02), 96% and 94.6%, 95% and 83.2% (p = 0.0045), 89.2% and 74.8% (p = 0.0021), 94.5% and 83.4% (p = 0.0058), and 91.1% and 79.6% (p = 0.0062), respectively.

On the other hand, Özyar *et al.* (79) did not show any improvement in LC in patients treated with additional BT implant after EBI as compared with EBI alone (3-year recurrence-free survival was 86% vs. 94%; p = 0.23). One explanation may be that the patients in the EBI alone arm were significantly younger and more likely to receive ChT (71.1% in contrast to 51.9% in the BT arm), which may have favorably affected their outcomes. Furthermore, patients received BT 4–6 weeks after EBI, which may have influenced the results due to a protracted overall treatment time. Neither did Rosenblatt *et al.* (81) in their study (n = 135) demonstrate a clinical advantage of adding a BT boost in the setting of locoregionally advanced NP tumors treated with cisplatin-based induction ChT and chemoRT (ChRT). Three-year OS was 62.9% and 63.3%, local recurrence-free survival rate was 60.5% and 54.4% for the standard vs. BT arm, respectively. Patients with advanced diseases (stages II–IV) were included in this study. As regard complications, Rosenblatt *et al.* (81) detected no differences in major toxicity between patients receiving EBI alone (21.6%) and patients receiving ICBT (24.4%). Leung *et al.* (80) reported (n = 257) a higher rate of grade 3–4 toxicities without BT (22%) vs. with BT boost (9%). On the other hand, Teo *et al.* (75), who in a detailed analysis involving 509 patients

Table 5
Results of BT for nasopharyngeal cancer

Author	*n* and T status or stage	BT and EBI dose (Gy)	Dose rate	LC (y)	OS (y)	Toxicity (grade 3–4)
Teo *et al.* (75)	163 T1:74 T2:89	18–24 (3 fr.) +60 EBI ±ChT	HDR (^{192}Ir)	94.5% (5 y)	86% (5 y)	6.13%
Syed *et al.* (76)	15 T1:1 T2:4 T3:6 T4:4	33–37 +50–60 EBI ±ChT	LDR (^{192}Ir)	93% (5 y)	61% (5 y)	NR
Levendag *et al.* (77)	91 T1-4	11 (3fr.)–18 (5 fr.) +60–70 EBI ± ChT	HDR (^{192}Ir)	96% (2 y) T1-2 67% (2 y) T3-4	80% (2 y) T1-2 67% (2 y) T3-4	NR
Chang *et al.* (78)	129 T1-2	5–16.5 (1–3 fr.) +64.8–68.4 EBI	LDR (^{60}Co)	93.9% (5 y) T1 79.5% (5 y) T1-2	85.8% (5 y)	9%
Özyar *et al.* (79)	106 T1:45 T2:32 T3:13 T4:16	12 (3 fr.) +58.8–74 EBI ±ChT	HDR (^{192}Ir)	86% (5 y)	NR	1%
Leung *et al.* (80)	145 T1:115 T2:30	10–12 (2 fr.) +66 EBI	HDR (^{192}Ir)	95.8% (5 y)	91.1% (5 y)	9%
Wan *et al.* (74)	213 T1:75 T2:45 T3:93	11 (2–3/fr.) IBT 14.8 (3–5) ICBT +63 EBI ±ChT	HDR (^{192}Ir)	95.9% (5 y)	95.2% (5 y)	2.4% (IBT) 4.7% (ICBT)
Rosenblatt *et al.* (81)	135 T3-4 & N2–3 = 36 others (III–IV) = 99	11 (LDR) 3 × 3 (HDR) ±ChT	LDR/HDR (^{192}Ir)	54.4% (3 y)	63.3 (3 y) 60.1 (3 y) T1-2 46.3 (3 y) T3-4	24%

n = number of patients; BT = brachytherapy; EBI = external beam irradiation; T = tumor; LC = local control; OS = overall survival; y = years; LDR = low-dose rate; HDR = high-dose rate; ChT = chemotherapy; NR = not reported; fr. = fraction; IBT = interstitial brachytherapy; ICBT = intracavitary brachytherapy.

compared the side effects of conventional EBI and EBI + BT, found the rate of chronic NP radiation ulceration to be 6.13% vs. 0.9%, with or without BT, respectively. However, the rates of epistaxis and bloody nasal discharge were comparable between the two groups. There was no increase in temporal lobe radiation encephalopathy (clinical or radiological), pituitary endocrine dysfunction, optic nerve and/or chiasma radiation injury or radiation-induced cranial nerve palsy.

Wan *et al.* (74) found that IBT boost may be a promising therapeutic choice for deep-seated residual NP cancer. A total of 213 patients with residual tumor (T1-T2ab) were treated with endoscopically guided ICBT (carcinoma located ≤1-cm below the nasopharyngeal epithelium) or IBT (deep-seated residual tumor located >1-cm below the epithelium). The IBT boost group had a higher ratio of T2b (81.0% vs. 34.5%) cases. The LC and OS rates were similar in the two groups (97.4% vs. 94.4% and 96.8% vs. 93.6%, respectively). The acute and late toxicity rates were similar in the two groups. But the authors concluded that if the tumor is bulky, IBT dosage optimization and distribution might be compromised, leading to a poor LC rate for persistent lesions.

Representative treatment results are summarized in Table 5.

Postoperative, perioperative, and intraoperative BT

If surgery is the preferred option, BT can be delivered alone in small tumors (OC T1-2N0 with high risk of local recurrences) or combined with EBI in case of the following factors: primary tumor size > 20–30 mm, close (<5 mm) or positive resection margin, positive lymph nodes, vessel invasion, and grade 3 histology (3, 48). There is a time gap (usually weeks) between the surgery and the implantation of the former tumor bed area. In the material of Lapeyre *et al.* (83), T1-4N0/positive cases (n = 82) with positive or close surgical margin of floor of mouth and mobile tongue cancer were analyzed. In stage T1-2N0, postoperative BT (60 Gy LDR) gave results (5-year LC 88%, OS 75%) similar to those produced by the EBI + BT (48 + 24 Gy LDR) combination (5-year LC 92%, OS 70%). BT was 3 weeks after EBI. They concluded that for T3-4N0/positive tumors EBI + BT is the accepted approach, but in T1-2N0 cases, sole BT is better for the protection of normal tissues, avoiding xerostomia. An independent influence was identified by Grabenbauer *et al.* (84) in oral and oropharyngeal cancer for UICC stage with stage I/II being associated with a local tumor control of 92 ± 4% and stage III/IV patients having a control rate of 65 ± 6% (p = 0.005). Representative results of postoperative EBI + BT are summarized in Table 6.

Table 6
Results of postoperative BT

Author (localization)	*n* and T status or stage	BT and EBI dose (% of patients)	Dose rate	LC (y)	OS (y)	Toxicity
Lapeyre *et al.* (83) (oral tongue, floor of mouth)	82 T1:29 T2:29 T3:10 T4:14	50–67 alone (44%) or 12–35 + 40–51.5 EBI (56%)	LDR (^{192}Ir)	81% (5 y)	68% (5 y)	10% G3
Grabenbauer *et al.*(84) (oral tongue, floor of mouth, base of tongue, tonsil)	145 I–II:53 III–IV:92	14–36 + 50–60 EBI	LDR (^{192}Ir)	78 ± 4% (5 y)	NR	7.5% STN and ORN
Strnad *et al.* (85) (oral cavity, oropharynx)	385 T1:172 T2:167 T3:17 T4:14 (Tx:15)	57 alone (63.9%) or 24 + 55 EBI (36.1%) ±ChT	PDR (^{192}Ir)	85.8% (5 y)	68.9% (5 y)	10.2% STN and 4.9% ORN

n = number of patients; T = tumor; BT = brachytherapy; EBI = external beam irradiation; LC = local control; OS = overall survival; y = years; LDR = low-dose rate; PDR = pulsed-dose rate; ChT = chemotherapy; NR = not reported; G = grade; STN = soft-tissue necrosis; ORN = osteoradionecrosis.

Perioperative BT is a type of postoperative BT where inactive applicators are implanted intraoperatively—during surgical excision—followed by a postoperative, fractionated treatment. Martínez-Mongue *et al.* (86–88) found a correlation in various sites between margin status and LC. Patients with high-risk margins (close <1 mm/positive) had a 9-year LC rate of 68.0%, whereas patients with wider margins had a 9-year LC of 93.7% ($p = 0.045$). They found that patients with high-risk margins, lymphovascular space invasion status, and recurrent disease have a higher risk of treatment failure, and the rate of grade ≥4 complications were more frequent in patients with posteriorly located implants ($p = 0.046$), perineural involvement ($p = 0.042$), prior irradiation ($p = 0.004$), implants with TV_{150} values greater than 13 mL ($p = 0.007$), and treatment at low doses ($p = 0.024$). The authors concluded that 2 Gy equivalent (Eq2Gy) doses ≥70 Gy may compensate the effect of close margins (1–5 mm) but do not counterbalance the detrimental effect of unfavorable (positive/close <1 mm) resection margins. No impact of margin status on LC was observed in patients treated at lower Eq2Gy doses of 50 Gy with perioperative HDR BT alone. Teudt *et al.* (89) concluded that due to the limited penetration of the radiation, typically 0.5–1 cm, extensive surgery is sometimes required. Some representative results are summarized in Table 7.

Intraoperative BT (IOBT) is the application of BT with single fraction to the tumor bed, while the area is exposed during surgery. IOBT is typically a component in the multidisciplinary treatment of locally advanced and recurrent cancer, in combination with EBI, surgery, and ChT. Advantages of IOBT are the ability to deliver an effective dose directly to tissue at-risk with visualization of the treatment target intraoperatively and to directly apply the applicator to the target in an anesthetized patient, which makes the possibility of a geographic miss highly unlikely (90). This technique was developed in the late 1980s in an attempt to combine the dosimetric advantages of HDR BT with the challenges of treating some complex anatomic surfaces with IORT. Use of flexible catheters for covering the target volume (surface) is necessary in this treatment method (91). HDR-IOBT can also treat very large and convoluted surfaces.

Representative result with the combination of EBI + BT is shown in Table 8.

Table 7
Results of perioperative BT

Author (localization)	*n* and T status or stage	BT and EBI dose	Dose rate	LC (y)	OS (y)	Toxicity
Martinez-Mongue *et al.* (87) (various)	103 I–IV primary: 50 recurrent: 53	32–40 alone (45%) or 16–24 (4/fr.) +45 EBI (55%) ±ChT	HDR (^{192}Ir)	68.6% (9 y; BT) 83.3% (9 y; +EBI)	38.3 (9 y; BT) 55.2 (9 y; +EBI)	24% G4
Teudt *et al.* (89) (paranasal sinus and nasalcavity)	35 (I–IV; 43%) primary: 22 recurrent: 13	10–35 (2.5/fr.) after resection ±40–63 EBI ± ChT	HDR (^{192}Ir)	67% (5 y)	72% (5 y)	0% N

n = number of patients; T = tumor; BT = brachytherapy; EBI = external beam irradiation; LC = local control; OS = overall survival; y = years; HDR = high-dose rate; ChT = chemotherapy; fr. = fraction; G = grade; N = necrosis.

Table 8
Results of intraoperative BT

Author (localization)	*n* and T status or stage (% of patients with EBI)	BT and EBI dose	Dose rate	LC (y)	OS (y)	Toxicity
Nag *et al.* (92) (various sites)	65 (71%) primary: 53 recurrent: 11 metastatic: 1	After resection 7.5–12.5 (1fr.) ±40–50 EBI ± ChT or 15–20 (1fr.)	HDR (^{192}Ir)	59% (5 y)	42% (5 y)	0% N

n = number of patients; BT = brachytherapy; EBI = external beam irradiation; T = tumor; LC = local control; OS = overall survival; y = years; fr. = fraction; HDR = high-dose rate; ChT = chemotherapy; N = necrosis.

Discussion

Despite numerous reports demonstrating the effectiveness of BT in the H&N region, this method has been used less commonly in recent years probably because concurrent ChT has been proven effective in controlling localized tumors. Combined ChT and RT have proved to be very effective as primary therapy in the management of advanced squamous cell carcinoma of the H&N (12, 21, 23). The final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial, comparing RT and ChRT applying carboplatin and/or cisplatin, showed a 23% better LRTC in stage III and IV OP cancer. However, grade 3 to 4 complications occurred in 56% vs. 30%, in favor of the exclusive RT group (93). Pederson *et al.* (94) treated 127 patients with stage III or IV BOT cancer applying paclitaxel-5-FU-hydroxyurea in combination with EBI. Forty-one percent of the patients had T4 tumor. Five-year LRTC and OS were 87% and 58%, respectively. In NP cancer, the Intergroup Study 0099 protocol showed ChT to be superior for advanced stages with respect to progression-free survival and OS (95). Hui *et al.* (96) demonstrated in stage III–IV an OS benefit with cisplatin-docetaxel induction ChT when compared with ChRT alone.

In the former BT studies, ChT was not used, or only occasionally was used, but from the beginning of this century, it became an integral part of the therapy. In BOT tumors, Cano *et al.* (34) applied ChRT followed by HDR BT boost. ChT consisted of carboplatin and/or paclitaxel or cisplatin/5-fluorouracil (5-FU) or mono carboplatin, cisplatin, or 5-FU. Three-year LRTC, OS, and CSS were 79.9%, 80.8%, and 69.5%, respectively. In the material of Takácsi-Nagy *et al.* (7), 28% of the patients received concomitant (cisplatin) ChT during EBI and compared with RT + BT alone better OS (69% vs. 39%; $p = 0.005$) was detected. In NP tumors, Levendag *et al.* (77) indicated neo-adjuvant ChT in conjunction with high cumulative doses of RT (81 Gy) for locally advanced T3-4 tumors because LC and OS at 2 years were 67% and 67% vs. 20% and 12% with or without ChT, respectively. These studies emphasize the role of ChT in the treatment of the NP.

In selected patients with H&N cancer in previously irradiated areas, PDR BT alone with concomitant ChT was applied. This combination seems to be feasible, safe, and the results are encouraging (97, 98).

In the years past beside the widely applied ChT, there was a significance technological development in RT. The aim in the therapy is, beside improving of the tumor control, to minimize the treatment-related toxicity. IMRT is also an alternative option for local dose escalation allowing superb coverage of the tumor target while decreasing the dose delivered to the surrounding normal structures. IMRT has been shown to improve LC and QOL by sparing the adjacent normal organs (99–101). In a meta-analysis of Beadle *et al.* (102), a total of 3172 patients with H&N cancer were identified as treated with IMRT or non-IMRT. They found a statistically significant improvement in CSS (84.1% vs. 66.0%; $p < 0.001$). IMRT's greatest justified advantage is the reduction of severe xerostomia compared with conventional EBI (101). In the phase III study of Nutting *et al.* (101) ≥grade 2, xerostomia was significantly less common with IMRT (29%) than with conventional RT (83%, $p < 0.0001$). Another advantage is the moderation of dysphagia with protection of pharyngeal constrictors (103). Levendag *et al.* (104) reported a sharp increase in the risk of the late dysphagia of approximately 19% per 10 Gy, beyond a mean dose of 55 Gy in superior and middle constrictor muscles. A disadvantage of IMRT is the very strict target volume definition which is necessary to avoid geographic miss. Organ motion during swallowing, target delineation because of dental artifact and interoperative and intraoperative variability in target delineation can influence its accuracy (105).

SRT therapy for H&N cancer was initially used in the spatially more rigid base of skull or nasopharyngeal region, but most recently, more groups and institutions are exploring the use of SRT in H&N sites outside the base of skull. It is applied as a boost after conventional EBI, and also as reirradiation in recurrent or second primary H&N cancer allowing precise delivery of tumoricidal doses of radiation with acceptable toxicity (106, 107).

Over the past decade, robotic surgery has opened new horizons in minimally invasive procedures in T1-T2 tumors of the retromolar trigone, BOT, tonsil, and soft palate. Transoral robotic surgery has emerged as a technique that allows H&N surgeons to safely resect large and complex OP tumors without dividing the mandible or performing a lip-split incision. Transoral robotic reconstructive surgery (TORRS) whether using free flaps, local flaps, or primary

closure appears to be a superior approach in select cases (selected larger lesions also) and holds the promise of expanding indications for minimally invasive reconstructive procedures. Plastic surgeons face a considerable reconstructive challenge as they attempt to contour and inset vascularized tissue in a highly anatomically restricted field, limiting both dexterity and visualization. This technique can offer the benefits of LRTC without the complications associated with open access or high-dose ChRT. The limitations of TORRS are additional time, staff, and experience (108).

Nowadays, there is an effort for treatment deescalation in H&N cancers to decrease treatment-related—late—toxicity. BT can be a very effective treatment alone or combinated with the above-mentioned modalities in this endeavor. Perioperative HDR BT combined with TORRS is a further step for successful treatment of recurrent disease.

Another reason for avoiding overtreatment is HPV in the epidemiology. High p16 expression results in a better response to ChRT and shows better long-term survival and seems to be a stronger prognostic marker than primary tumor extension, lymph node involvement, distant metastases, and clinical stages (109, 110). Further investigations are necessary to define the optimal treatment of this patient population.

In OC cancer, recent data have shown that IMRT (with or without concurrent ChT) resulted in an LC rate of approximately 60% when including advanced-stage (inoperable) disease cases (111). Compared with these IMRT data, BT ± EBI in several studies showed a better outcome with a 5-year LC rate of 67–94%. Sresty *et al.* (112) compared IBT with IMRT with respect to treatment planning by designing and evaluating both in 15 patients with tongue cancer. Better planning results were obtained in tongue cancers, treated with BT vs IMRT. The average dose conformity index was 1.063 and 1.092, respectively. BT provided the same dose conformity, but a lower spinal cord dose and shorter planning time.

Studies applying IMRT in OP tumors reported a 5-year LC rate of 86–92% and OS rate of 76–87%. STN and ORN were detected in 2–6% and 1–4%, respectively (113–116). The rate of T4 cases in the IMRT studies varied between 11% and 29% (mean 20%) and most of the patients received ChT. Results with EBI + BT in OP cancer with the exception of BOT (mostly T1-2 and rarely T3 tumors) showed an LC and OS rate of 75–87% and 60–64%, respectively (Table 4). In comparisons of IMRT data with the EBI + BT results in cases of BOT cancer (LC and OS 64–89% and 26–87%; Table 1), IMRT seems to yield better results than BT (7, 13–19, 25–28, 30–34, 36, 113–116). There is a possible explanation for these findings. In the BT articles, the rate of T4 tumors was higher (mean 27%), treatment planning was seldom conformal and patients generally did not get ChT, which can improve the LRTC in OP cancers by 23% (93).

There are data supporting the use of IMRT followed by an interstitial implant to further reduce the dose to adjacent normal tissue. In the analyses of Teguh *et al.* (117), OP cancer was boosted after 46 Gy EBI by IMRT, BT, or SRT (Cyberknife). Boosting with IMRT resulted in more dysphagia as opposed to BT or SRT. They reported a correlation between the dose received by the muscles of mastication and resulting trismus. Authors concluded that the lowest mean doses of radiation to the swallowing muscles were achieved when using BT as opposed to SRT or IMRT (118). Al-Mamgani *et al.* (24) published excellent results in 167 patients with 46 Gy IMRT ± ChT and 22 Gy BT (PDR) boost for OP tumors (T1-3). Patients who were not suitable for the standard BT boost were offered a boost by means of Cyberknife and in patients with T4 and large T3 tumors, a boost of 24 Gy was given by means of IMRT. The 5-year LC and OS rates were 94% and 72%, respectively. No grade 4 toxicity was reported. In the authors' opinion, BT boost is not suitable for tumors larger than 5 cm, or tumors adjacent to the mandible or great vessels, in cases of detected retropharyngeal node involvement, tumors located in the posterior pharyngeal wall or involving the parapharyngeal space. In another article by the same author, better QOL regarding dry mouth, swallowing, and opening mouth is reported using BT boost as against IMRT boost (119).

Chen *et al.* (120) reviewed the results of 102 patients with stage III–IV BOT cancer treated with IMRT (simultaneous integrated boost technique; $n = 45$) or EBI + BT ($n = 57$). The 5-year LC and OS rate for IMRT with SIB vs. EBI plus BT was 86% and 72% vs. 79% and 49%, respectively. It has to be noted that the proportion of patients receiving ChT was 97% vs. 26% in the IMRT and the BT group, respectively, so the subanalyses including cases treated with ChRT showed an LC rate of 86% vs. 87% and an OS rate of 72% vs. 67% for the IMRT and BT group, respectively. There were no significant differences in rates of overall or specific ≥ grade 3 toxicities among the treatment groups.

Currently, patients with NP cancer are treated with IMRT, sparing neighboring critical structures next to the NP, such as the brain, pituitary gland, optic chiasm, optic nerve, and spinal cord. Zheng *et al.* (121) retrospectively compared the outcome of three-dimensional (3D)-conformal RT and ICBT for residual disease, which was confirmed by biopsy 2–8 weeks after initial treatment. The 5-year OS and local failure-free survival for 3D vs. ICT groups were 65% vs. 56% ($p = 0.33$) and 89% vs. 76% ($p = 0.07$). For T3-4 tumors, the local failure-free survival was significantly better in the 3D group (84% vs. 61%, $p = 0.03$). The use of EBI + BT in case of advanced disease (T3-4) results in poorer LC and OS (77, 81). Yau *et al.* (122) retrospectively reviewed the records of 755 patients treated from 1994 to 2001. For residual tumors ICBT boost (20 Gy) or SRT boost (15 Gy) was delivered. The overall 3-year local failure-free control rate was still significantly lower for patients treated with BT (71% vs. 86%,

$p < 0.01$). The incidence of grade 3–4 side effects were similar in the two groups.

NP carcinomas may be irradiated with SRT (reirradiation) also with better control rates. Late severe toxicities yield up to 20–30%. Patient and tumor selection criteria (limited volume) and dose constraints to the carotids (cumulative dose 110 Gy or less, to avoid the risk of potentially lethal carotid blowout) must be carefully chosen. Fractionated regimens (at least five fractions) should be preferred (30 Gy in five fractions to 36 Gy in six fractions). SRT is also used as a boost after 46 Gy IMRT (123). Levendag *et al.* (124) studied the role of ICBT or SRT boost after EBI compared with cases treated by EBI alone. In the case of T1,2N + tumors, the local relapse rate was significantly smaller if a boost was applied (0% vs. 14%, $p = 0.023$). For advanced T-stages (T3,4N+,0), the reduction in local relapse rate (10% vs. 15%) was not significant ($p = 0.463$). Hara el al. (125) reported long-term outcomes in patients receiving SRT as a boost after EBI for locally advanced NP tumor (T4 38%). At 5 years, LC was 98%, OS 69%. Late toxicity included radiation-related retinopathy in 3, carotid aneurysm in 1, and radiographic temporal lobe necrosis in 10 patients.

The results of external beam reirradiation and SRT in recurrent NP cancer were better than that of BT for T3-4 tumors in the material of Stoker *et al.* (73). Levendag *et al.* (126) found better results in T1-2 tumors with ICBT, but offered an SRT boost in T3-4 because of better target coverage and sparing. However, compared to SRT—on the base of the literature—HDR BT provides a higher degree of intratarget dose heterogeneity with no upper dose limits and a sharper dose falloff gradients outside the target volume (118, 127, 128).

ORN is a serious consequence of radiotherapy in the H&N region. Peterson *et al.* (129) clarified the impact of cancer therapies on prevalence of ORN based on 43 articles selected between 1990 and 2008. The weighted prevalence for ORN was 7.4%, 5.1%, 6.8%, and 5.3% with conventional RT, IMRT, ChRT, and BT, respectively.

In the comparison of treatment modalities in OP and NP cancers by Teugh *et al.* (117), the lowest mean doses of radiation to the swallowing muscles were achieved with BT as opposed to SRT or IMRT.

Despite the very good results of BT, it is not used so widely because BT procedure requires special skills, continuing training, multidisciplinary cooperation, and a high level of expertise. Furthermore, it needs to be performed in dedicated centers with experience in this field. But analyzing the reimbursement of BT, the total mean cost seems to be the lowest for RT followed by BT when compared with surgery followed by RT or single-modality RT, possibly owing to fewer days of hospitalization and relapses (130). In a comparison with SRT (in liver lesions), HDR BT carries less cost to the Medicare system, although the difference is small (128).

Summarizing this review, however, there are some limitations of the available literature.

There are only a few direct comparisons of LDR and HDR techniques. Inoue *et al.* (57) and Kakimoto *et al.* (131) found no significant difference—in tongue and floor of mouth tumors—regarding LC, soft-tissue, and bone necrosis, though the former published slightly better LC with HDR ($p = 0.113$). In spite of similar results with indirect comparisons in other localizations, further studies are needed (7, 33, 34).

Quantitative, dosimetric analysis of different BT treatment plans is very difficult due to the lack of widely accepted quality parameters. Most authors do not publish the required data: size of the target volume (cm^3), V_{100} (the volume that receives 100% of the reference dose), V_{150} (the volume that receives 150% of the reference dose), DNR (dose nonuniformity ratio, V_{150}/V_{100}) and coverage index (the fraction of the target volume that receives a dose equal to or greater than the reference dose), conformity index (conformity index showing how well the reference isodose encompasses the target volume and excludes nontarget structures), homogeneity index (homogeneity index measuring the fraction of target volume receiving dose in the interval of 1.0–1.5 times the reference dose), external volume index (the ratio of the normal tissue volume outside the planning target volume [PTV] receiving a dose equal to or greater than the reference dose, to the PTV), overdose volume index (the fraction of PTV receiving a dose equal to or greater than twice the reference dose) (132–135). There are only a few studies providing some of these data (17, 19, 27, 30, 53, 58, 68, 70, 85, 87, 92). Some of these parameters, for example the target coverage by the reference dose, are very important for further analyses regarding correlations with recurrence. In the study of Vedasoundaram *et al.* (53), patients with better coverage index and conformity index showed a trend to complete response compared to those with residual disease.

Another problem is the lack of standards in BT (target definition, doses, fractions, dose prescription, and so forth). There are two available recommendations, one European and one American (3, 4). In OC cancers, it is recommended to apply 25–30 Gy after 40–50 Gy EBI (3, 136). For OP tumors, the boost BT dose recommendation is 25–35 Gy with LDR and/or PDR and 21–30/3 Gy or 20–24/4 Gy with HDR after 45–50 Gy EBI (3). The recommended dose of NP cancer for T1 (ESTRO recommendation), for T1-3 (ABS recommendation) tumor is 60 Gy EBI and after a rest period of 1–2 weeks 18/3 Gy/6 fractions/3 days, for T2-4 (ESTRO) and for T4 (ABS) 70 Gy EBI and 12/3 Gy/4 fractions (3, 4). Postoperatively, the dose is 10–25 Gy as a boost after EBI (3, 48). It is advisable to maintain the dose rate in LDR between 0.3 and 0.6 Gy/h and in PDR between 0.3 and 0.7 Gy/h (3). If the dose rate was >0.7 Gy/h, the risk of necrosis was higher (47). In HDR technique generally, 3–4 Gy/fraction is advised and applied (3, 4). It is

important to keep the implants more than 5-mm away from the mandible to avoid ORN and spaced 10−12 mm apart to decrease the risk of STN (1). The suggested interval between EBI and BT is not longer than 20 days, avoiding the decreasing of LC because of repopulation (137).

Conclusions

BT is generally an invasive but very effective method for delivering doses accurately, allowing at the same time the maximal protection of surrounding normal tissues and the preservation of organ function. Compared with new techniques (IMRT, SRT), BT provides excellent dose conformity but lower spinal cord dose and shorter planning time. With the advent of new technologies, results can be improved with the combination of IMRT and BT applying stepping source HDR and/or PDR BT, which offers individually optimized target dose distribution including local dose escalation complementary to EBI. Further studies are needed to compare LDR and/or PDR vs. HDR methods in different sites with uniform dose and dose prescription for the correct analysis. However, in advanced, selected (mainly NP tumors) T3 and extended T4 diseases (tumor >5 cm, adjacent to the mandible or great vessels, detected retropharyngeal node involvement, tumor located in the posterior pharyngeal wall involving the parapharyngeal space or the bone) in the H&N region, IMRT, or SRT—because of the optimal coverage of the target volume—can appear to be a better choice than BT but with perioperative BT this disadvantage can be compensated.

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