

Modern head and neck brachytherapy: from radium towards intensity modulated interventional brachytherapy

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Abstract

Intensity modulated brachytherapy (IMBT) is a modern development of classical interventional radiation therapy (brachytherapy), which allows the application of a high radiation dose sparing severe adverse events, thereby further improving the treatment outcome. Classical indications in head and neck (H&N) cancers are the face, the oral cavity, the naso- and oropharynx, the paranasal sinuses including base of skull, incomplete resections on important structures, and palliation. The application type can be curative, adjuvant or perioperative, as a boost to external beam radiation as well as without external beam radiation and with palliative intention. Due to the frequently used perioperative application method (intraoperative implantation of inactive applicators and postoperative performance of radiation), close interdisciplinary cooperation between surgical specialists (ENT-, dento-maxillary-facial-, neuro- and orbital surgeons), as well interventional radiotherapy (brachytherapy) experts are obligatory. Published results encourage the integration of IMBT into H&N therapy, thereby improving the prognosis and quality of life of patients.

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Purpose

Head and neck (H&N) is one of the most challenging anatomic sites of the human body. Both regional anatomy and physiology are uniquely complex and the basic functions of speaking, hearing, seeing and swallowing, as well as smelling, are concentrated in this area of the body. An additional difficulty is that a H&N implant is technically challenging. The procedure requires special skills and continuous training, including the ability to organize and perform multidisciplinary applications with a high level of expertise.

The appearance and function of the H&N are critical to an individual's self image. The treatment of H&N cancer at any cost without trying to reduce treatment related toxicity is no longer an accepted strategy. In the modern era, H&N cancer management requires interdisciplinary thinking and multidisciplinary approaches [1-5].

Head and neck is one of the few anatomic sites where locoregional control of the cancer plays such an important role in ultimate survival. Much of the failure patterns after H&N cancer treatments are local and regional rather than systemic. Distinct from most other sites, in H&N cancer patients lymph node (LN) treatment affects not only regional control, but also influences survival. A large cohort

data analysis showed that local control (LC) was the most significant variable affecting the development of distant metastasis in patients with the most common H&N cancers [6]. If local and regional control are important and brachytherapy represents a better method of delivering effective therapy to a biologically significant target compared to other treatment options, brachytherapy should also be important. However, in the absence of mature phase III trial results or other high level evidence, this remains the belief of a small group of enthusiastic experts in the field.

Both primary and recurrent squamous cell carcinoma of the H&N are classic indications for brachytherapy. A high rate of local tumor control at the cost of limited morbidity can be achieved with brachytherapy through good patient selection, meticulous source implantation, and careful treatment planning [7].

Interstitial brachytherapy is ideal for selectively delivering a high dose exclusively to the primary tumor volume, thus minimizing treatment related toxicity. Considerable experience has been accumulated with low-dose-rate (LDR) brachytherapy in the treatment of carcinoma of the lip, tongue, floor of the mouth, oral mucosa, base of the tongue, tonsillar region, soft palate, nasophar-

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ynx, etc. [8]. Analyses of large clinical series have demonstrated the effectiveness of this treatment method, but also indicate that LDR brachytherapy modalities should be optimized to increase the therapeutic ratio. Low-dose-rate brachytherapy is now challenged by high-dose-rate (HDR) brachytherapy and pulsed-dose-rate (PDR) brachytherapy [9]. High-dose-rate/PDR stepping source technologies offer the advantage of optimizing dose distribution by varying dwell times. Preliminary and mature results obtained with these two latter modalities are now available [10,11]. However, important knowledge on brachytherapy target definition rules, as well as on the importance of optimal implantation geometry remain obligatory. Pernot *et al.* [12] proved the importance of a safety margin around the tumor surface (CTV is smaller than PTV) after analysing the outcome of 448 tongue cancer implants, and Siebert *et al.* stated the importance of the use of the Paris System geometry in individually optimized dose distributions [13].

On the other hand, in the early 90ies, interdisciplinary cooperation with surgical specialities during perioperative implantations (intraoperative implantation of inactive applicators combined with complete or incomplete surgical resection, followed by a postoperative volume optimized treatment planning and fractionated radiation procedure) already opened up a new era in function/cosmesis preserving interdisciplinary H&N cancer treatments [14-17].

In the following, a literature overview is presented according to the published results in different H&N anatomy sites.

Cancer of the lip

Squamous cell cancers (SCC) of the lip are one of the oldest indications for interstitial radiotherapy [18]. Following excellent results with LDR/PDR brachytherapy [19-24], Guinot *et al.* introduced HDR treatments resulting in excellent outcome and low toxicity [25] and published long term outcome data [26]. Also Ayerra *et al.* stated the meaningful switch from linear sources to stepping

source technology [27]. Representative treatment results of large cohorts are summarized in Table 1.

The most common treatment related side effects are ulcers/superficial necroses, which are very rare under a dose of 50 Gy, and were observed with a strong dose dependency in 5-8% of patients in the dose range of 50-100 Gy. Over 100 Gy, there is a nearly 30% probability of ulceration. Dose rate was also found to be a significant risk factor for ulceration [28].

Comissural location results in an eight fold higher rate of functional disturbances (4.2%) than were seen in the lower lip (0.5%) and upper lip (0.0%) cases. The size of the lesion is also an important factor: cosmetic and functional disturbances were observed 9 fold more frequently in T3 cancers (9%) than in T1 (1%) [19].

Oral cavity

Low-dose-rate brachytherapy of T1-T2 N0M0 lesions has been employed in the treatment of carcinoma of the mobile tongue, floor of the mouth, oral mucosa, and retromolar trigonum, and has been the successful gold standard for radiotherapy over decades [29-36]. However, due to the development of stepping source technology as well computed, cross sectional tomography (computed tomography/magnetic resonance imaging) based individually optimized treatment planning procedures, HDR/PDR brachytherapy has been expanded [37-43]. A recent meta-analysis of published data indicated that HDR brachytherapy is a comparable alternative to LDR brachytherapy in the treatment of oral cancer. The authors suggest: HDR brachytherapy might become a routine choice for early-stage oral cancer in the future [44]. Furthermore, data in the literature also underline the fact that neither young nor old age are negative prognostic factors for outcomes with brachytherapy in oral cancer [45,46].

The probability of both local control and toxicities are correlated with the target dose, as well as the dose to organs at risk (OAR). It is advisable to keep the target dose between 65-70 Gy in the case of brachytherapy

Table 1. Representative brachytherapy results in lip cancer (LDR/HDR/PDR)

Author	n	Dose (Gy)	LDR	HDR	PDR	5 years local control (%)	5 years OS (%)	Toxicity
Beauvois <i>et al.</i> [21]	237	65-68	¹⁹² Ir	–	–	95	74	9.5% necrosis
Gerbaulet <i>et al.</i> [22]	231	76	¹⁹² Ir	–	–	95	n.d.	13.0% necrosis
Tombolini <i>et al.</i> [24]	57	62	–	HDR	–	90 (10 yrs)	n.d.	n.d.
Guinot <i>et al.</i> [26]	104	9 × 5.0 bid	–	HDR IMBT	–	95.2	64.4	0%
Lock <i>et al.</i> [173]	51	55	¹⁹⁸ Au	–	–	97.8	87.9	Good cosmesis 48/51
Serkies <i>et al.</i> [25]	32	60-70	–	–	PDR	98		2/32
Johannson <i>et al.</i> [20]	43	60	–	–	PDR	94.5 (10 yrs)	58.9 39.1 (10 yrs)	2% soft tissue necrosis 2% bone necrosis

LDR – low-dose-rate, HDR – high-dose-rate, PDR – pulsed-dose-rate, OS – overall survival, bid – twice a day fractions (min. 6 hours interval), 10 yrs – 10 years data, IMBT – intensity modulated brachytherapy

monotherapy, between 60-65 Gy in the adjuvant setting following R0 resections, and between 10-25 Gy in the case of a local boost complementary to external beam therapy (EBRT) [47]. A dose rate of > 0.7 Gy/h was associated with a higher risk of necrosis [31], whilst a total combined dose of > 80 Gy (EBRT + implantation) resulted in improved outcome data [55]. If the resection margins were not clear, patients with a postoperative dose of > 68 Gy had significantly less local recurrences [48]. In addition, it has been proven that custom made protection materials (distance and/or lead protectors) reduce the severity of OAR toxicity [49] – if no individual dose conformation on the OAR's is performed.

Most of the published series report local recurrence rates in T1/T2/T3 cancers of 0-7%/20-25%/45-80%, respectively (Table 2). The most common late toxicities are ulceration (3-25%) and tongue hemiatrophy (G1/G2: 70%). The development and course of mucosal reaction are slightly faster with the use of HDR than with LDR/PDR, although the peak time is similar at approximately

10 days postimplant [50]. Tongue atrophy is a very late developing side effect (> 72 months postimplant), and has a significant correlation with the treated volume. Nevertheless, most patients can usually maintain their activities of daily life without severe restriction [51].

Oropharynx cancer

Interstitial brachytherapy in the oropharynx is technically challenging and needs a high level of personal expertise. Experts were already disagreeing in the early 90ies about the role of brachytherapy in this entity [52-54]. Nowadays, brachytherapy is not often used to treat oropharyngeal cancers, because newer external radiation approaches, such as IMRT +/- chemotherapy appear to be very effective. However, analysis of large series have provided data indicating that the use of modalities such as LDR brachytherapy should be optimized in treating these tumors [55-58]. Early studies showed the feasibility of HDR/PDR compared to LDR in oropharyngeal carci-

Table 2. Representative brachytherapy results in oral cavity cancer (LDR/HDR/PDR)

Author	n	Anatomic site	Dose (Gy)	LDR	HDR	PDR	5 years local control (%)	5 years OS (%)	Toxicity
Pernot <i>et al.</i> [35]	552	Mobile tongue	70-75	¹⁹² Ir, wire	–	–	St. I: 95 St. II: 65 St. III: 54 St. IV: 36	St. I: 71 St. II: 43 St. III: 33 St. IV: 23	Grade I: 20% Grade II: 9% Grade III: 4% Grade IV: 0.2%
Pernot <i>et al.</i> [35]	207	Floor of mouth	70-75	¹⁹² Ir, wire	–	–	St. I: 97 St. II: 73 St. III: 64 St. IV: 0	St. I: 74 St. II: 46 St. III: 39 St. IV: 0	Grade I: 20% Grade II: 9% Grade III: 4% Grade IV: 0.2%
Yoshida <i>et al.</i> [46]	70	Mobile tongue	70	¹⁹² Ir ²²⁶ Ra ⁶⁰ Co	–	–	78 71 (10 yrs)	80 CSS 72 (10 yrs) CSS	n.d.
Inoue <i>et al.</i> [39]	58	Mobile tongue	6 × 10	–	HDR	–	T1/T2 = 82/79	T1/T2 = 83/82, CSS	10%
Inoue <i>et al.</i> [39]	341	Mobile tongue	70	¹⁹² Ir ²²⁶ Ra	–	–	T1/T2 = 85/80	T1/T2 = 85/79, CSS	6%
Marsiglia <i>et al.</i> [49]	160	Floor of mouth	60-70	¹⁹² Ir, wire	–	–	T1/T2 = 93/88	76	18% bone necrosis 10% soft tissue necrosis
Strnad <i>et al.</i> [62]	67	Floor of mouth	50-64	–	–	PDR 24 hours	Approx. 87	Approx. 77	9.7% soft tissue necrosis 7.2% bone necrosis
Strnad <i>et al.</i> [62]	103	Mobile tongue	50-64	–	–	PDR 24 hours	Approx. 78	Approx. 67	9.7% soft tissue necrosis 7.2% bone necrosis
Guinot <i>et al.</i> [43]	50	Mobile tongue	11 × 4	–	HDR IMBT bid	–	79	70	4% bone necrosis 16% soft tissue necrosis
Yamazaki <i>et al.</i> [45]	80	Mobile tongue	6 × 10	–	HDR bid	–	T1/T2/T3 82/79/89	T1/T2/T3, CSS 86/781/89	T1/T2/T3 17%/20%/0%

LDR – low-dose-rate, HDR – high-dose-rate, PDR – pulsed-dose-rate, OS – overall survival, CSS – cause specific survival, bid – twice a day fractions (min. 6 hours interval), IMBT – intensity modulated brachytherapy

noma treatments [59-63]. Additionally, in the case of base of tongue cancers, mature reports in the literature stated the advantage of definitive radiotherapy versus surgery [64-66]. There are currently several factors supporting the use of modern intensity modulated brachytherapy (IMBT). It offers individually optimized brachytherapy target dose distribution including local dose escalation complementary to EBRT, better function preservation compared to aggressive EBRT, and economic advantages.

With highly sophisticated EBRT treatments using the latest technology, the majority of local recurrences were found within the 100% dose area. As a result, the need for further local dose escalation was raised [67], and interstitial brachytherapy was proven to be the most optimal method to achieve this aim [68].

The lower toxicity advantage associated with the use of IMRT technology in EBRT (compared to 3D conformal techniques) can optimally be paired with the excellent local dose escalation potential of interstitial IMBT [69]. This theory was also supported by the knowledge obtained, when IMBT and EBRT patients were evaluated independently in a bivariate model. The IMBT patients fared significantly better than the EBRT patients [69]. Future comparative and prospective clinical trials are needed to confirm this observation. A further advantage of local dose escalation by IMBT is less target movement during the course of radiation compared to EBRT, especially if highly conformal (minimal security margins around the CTV) external beam techniques are used [70]. A strong argument for advising IMBT alone or as a part of multimodality treatment for oropharyngeal carcinomas is the published favorable long-term outcome data [71-79]. Usually, LC rates of 65-90% are independent of tumour stage, but do depend on patient selection, dose level of the combined EBRT, and combination with chemotherapy. The combination of EBRT and neck dissection accounts for the high likelihood of regional control in most published series [80]. Representative outcome details are presented in Table 3.

Nasopharynx cancer

Since the early days of radiotherapy, irradiation with or without chemotherapy, has played an important role in the treatment of nasopharynx cancer (NPC) [81,82]. High dose EBRT alone cured many patients, but often at the expense of severe late toxicities [83]. When local control was proven to be an independent prognostic factor for the development of distant metastases [84], combined EBRT + brachytherapy treatments were introduced and a dose-tumor control relationship was realized [85]. Many authors reported a successful combination of EBRT with an intracavitary brachytherapy boost as local dose escalation. However, the treatment only presented excellent results in small T-stage cancers [86-94].

Brachytherapy represents a valuable therapy option, not only in primary NPC, but also in carefully selected locally recurrent disease [95,96]. The introduction of chemo-radiotherapy, significantly enhanced the outcome especially in locally advanced disease [97,98]. Chemotherapy as well as high-technology treatment techniques for advanced NPC obviously increases the treatment costs.

However, the costs generated by conventional treatment schemes and modalities in other head and neck tumor sites are in a similar range [99]. Most of the publications represent results of descriptive statistical evaluations of monoinstitutional patient cohorts. To answer the question if brachytherapy boost in combination with EBRT and chemotherapy improves the outcome in loco-regionally advanced NPC, a prospective randomized trial led by the International Atomic Energy Agency (IAEA) was performed [100]. The study results showed no statistical difference between the use of brachytherapy or external radiochemotherapy alone. However, in a different analysis by the Rotterdam group, which contained parts of the IAEA trial cohort, significant differences in local control were found between patients treated with or without a brachytherapy boost in the pooled analysis for T1-T2 N+ tumors, thus confirming the results of previous studies for patients with early local disease [101,102]. The authors stated that for the applied cumulative dose level (81 Gy), the IMRT or stereotactic (SRT) boost method was associated with better outcomes in $\geq T3$ disease. One can speculate that in the case of larger tumors, the intracavitary implantation technique resulted in geometrical failure on the target. These thoughts seem to be supported by the excellent outcome results of endoscopically guided combined intracavitary + interstitial implantations, where IMBT boost was found to be a promising therapeutic solution for deep-seated residual NPC [103]. A selection of treatment results is presented in Table 4.

Intra- and perioperative implantations (IOBT and POBT)

The idea to combine surgery and immediate (intraoperative) brachytherapy is not new. Early use of radium and later LDR Ir-192 or I-125 implants have already played an important role in cancer treatments [104-113]. The integration of cross sectional imaging into brachytherapy dose planning [114,115] made it possible to introduce IMBT in the perioperative and fractionated settings [116-122]. Later, the techniques of intraoperative placed flaps and single shot radiation by means of individual dose painting methods also became available [123,124]. Due to these developments, it became possible to treat local tumor masses successfully with less toxicity compared to wide field EBRT [125] or reduce the radicality of surgical resections in order to preserve function [126-128]. Although intraoperative brachytherapy is an appealing interdisciplinary treatment alternative, higher complication rates in patients undergoing microvascular free tissue transfer have been reported. However, this should not deter or alter the aggressiveness of cancer therapy used for advanced/recurrent H&N cancer [129,130]. If one speculates, the radiobiological and dose painting advantage of fractionated perioperative IMBT compared to single shot intraoperative techniques may result in further toxicity reduction in future studies. Also in recurrent cancers of the neck, best results were obtained with perioperative brachytherapy in combination with surgical excision and reconstruction of the skin using a vascularized myocutaneous flap. This resulted

Table 3. Representative brachytherapy results in oropharynx cancer (LDR/HDR/PDR)

Author	n	Anatomic site	Dose (Gy)	LDR	HDR	PDR	5 years local control (%)	5 years OS (%)	Toxicity
Pernot <i>et al.</i> [35]	271	Tonsil, soft palate	70-75	¹⁹² Ir, wire	–	–	T1/T2/T3/T4 96/95/76/78	T1/T2/T3/T4 68/69/51/46	Grade I: 20% Grade II: 9% Grade III: 4% Grade IV: 0.2%
Pernot <i>et al.</i> [35]	90	Pharyngoglossal sulcus	70-75	¹⁹² Ir, wire	–	–	T1/T2/T3/T4 79/73/53/4 out 5*	T1/T2/T3/T4 60/45/23/0	Grade I: 20% Grade II: 9% Grade III: 4% Grade IV: 0.2%
Levendag <i>et al.</i> [59]	38	Soft palate, tonsillar fossa	40-66	–	1 fraction & bid	Daytime & 24 hours	87	60	2 × ulcers 3 × scarring 2 × severe pain
Nose <i>et al.</i> [63]	83	Soft palate, anterior pillar, posterior pillar, base of tongue, vallecula	48	–	bid	–	84	64	29% transient soft tissue necrosis
Takácsi Nagy <i>et al.</i> [71]	30	Base of tongue	EBRT 60 BT 12-30	–	10 × IMBT, bid	–	62	43	1% bone necrosis 3% ulceration
Johansson <i>et al.</i> [74]	83	Base of tongue	EBRT 50 BT 30	–	–	24 hours, PDR	89 85 (10 yrs)	65 45 (10 yrs)	10% permanent feeding tube 5% soft tissue necrosis
Cano <i>et al.</i> [76]	18	Base of tongue	EBRT 50 BT 24.5	¹⁹² Ir, seeds	–	–	89	52	11%
Gibbs <i>et al.</i> [79]	41	Base of tongue	EBRT 50 BT 26	¹⁹² Ir, seeds	–	–	82	66	5% bleeding 8% infection 7% soft tissue ulceration 5% bone necrosis

LDR – low-dose-rate, HDR – high-dose-rate, PDR – pulsed-dose-rate, OS – overall survival, bid – twice a day fractions (min. 6 hours interval), IMBT – intensity modulated brachytherapy, EBRT – external beam therapy, BT – brachytherapy, *At 3 years

in < 10% severe toxicities (fistulation, haemorrhage and wound break down) [131]. Selected results of H&N intra- and perioperative treatments are highlighted in Table 5.

Surface molds

The most frequently used H&N brachytherapy application form is the interstitial implantation. The majority of treatments with surface molds are for superficial malignomas on the skin (including the scalp) or those on the oral mucosa. While interstitial brachytherapy requires hospitalization, fractionated IMBT treatments based on customized mold and dental techniques can be per-

formed as an outpatient service. The use of custom made molds and IMBT are common and offer an advantage for patients, especially in complex anatomic locations such as the ear, the external auditory canal, the periauricular region, the gingiva or hard palate, the maxillary sinus, and the eyeless orbit, etc. [133-142]. Furthermore, superficial buccal or lip cancers can also be successfully treated with HDR/PDR mold treatments [143, 144]. Most of these are mold based monoplanar implants.

In certain situations (for example nasopharynx), the quality of the dose distribution of a brachytherapy boost complementary to EBRT can be improved by the use of anatomically customized mold-type applicators [145].

Table 4. Representative brachytherapy results in nasopharynx cancer (LDR/HDR/PDR)

Author	n	EBRT dose (Gy)	BT dose (Gy)	LDR	HDR	PDR	5 years local control (%)	5 years OS (%)	Toxicity
Teo <i>et al.</i> [85]	163	60	18-24	–	3 fractions intracavitary	–	94.5	86	6% ulceration 5% cranial nerve palsy 23% epistaxis/ BND
Lee <i>et al.</i> [92]	55	65 primary 39 recurrent	10-54 LDR 5-7 HDR	²²⁶ Ra ¹³⁷ Cs ⁶⁰ Co	2 fractions IMBT bid	24 hours	89 primary 64 recurrent	86 primary 91 recurrent	No G3/G4 toxicity
Leung <i>et al.</i> [95]	145	66	10-12	–	2 x weekly fractions	–	95.8	91.1	10.5%
Levendag <i>et al.</i> [101]	91	60-70	11-17	–	IMBT 11 Gy in 3 fx 17 Gy in 5 fx	–	T1-T2/T3-T4 96/67*	T1-T2/T3-T4 80/67*	n.d.
Ren <i>et al.</i> [154]	40	60	16	–	IMBT	–	97.5	92.5 DFS	5 pts hearing impairment 7 pts ulceration
Wu <i>et al.</i> [88]	175	58	20	–	IMBT bid	–	94 (10 yrs)	71.7 (10 yrs)	11% cranial neuropathy 2.3 % ulceration 1% temporal lobe necrosis
Rosenblatt <i>et al.</i> [100]	135	70	11 Gy LDR 3 × 3.0 Gy HDR	¹⁹² Ir, wires	IMBT	–	54.4 (3 yrs)	63.3 (3 yrs)	33 out of 135 G3/G4
Wan <i>et al.</i> [103]	171 ICBT 42 IBT	63	14 ICBT 11 IBT	–	IMBT	–	94.4 ICBT 97.4 IBT	93.6 ICBT 96.8 IBT	4.7% late G3/4 in ICBT 2.4% late G3/4 in IBT

EBRT – external beam therapy, LDR – low-dose-rate, HDR – high-dose-rate, PDR – pulsed-dose-rate, IMBT – intensity modulated brachytherapy, BT – brachytherapy, ICBT – intracavitary brachytherapy, IBT – interstitial brachytherapy, DFS – disease free survival

Palliative treatments

Cure or overall survival may not be the ultimate goal in palliative treatments, and as such, surgery as well as systemic agents and radiation are important means of locoregional control [146]. Phase III study results indicate that postoperative full-dose EBRT reirradiation combined with chemotherapy after salvage surgery significantly improved disease free survival, but had no significant impact on overall survival. Regarding toxicity, an increase in both acute and late toxicity was observed [147]. The palliative effect of a given treatment is strongly correlated with the prolongation of the survival time, and may contribute to improving the remaining survival time in patients with metastatic/advanced cancer with a poor performance status [148]. Brachytherapy is ideal for palliation in nearly all anatomic sites and has excellent outcome data, independent of the applied form of brachytherapy (LDR/HDR/PDR) [120,149-165]. Compared to external beam reirradiation series [159], IMBT offers significantly better local control rates.

Dose and fractionation, documentation and combination with external beam therapy (+/- chemotherapy)

By using the classical Paris System and Ir-192 wires or seed implants, the dose distribution could be forecast when performing the implant [166]. Furthermore, the Paris System has demonstrated its practicability in many clinical situations in large cohorts and over a long time. There is mature experience in the literature that total dose of a successful radiation therapy depends on many factors, including tumor and surrounding normal tissue radiosensitivity, size of target volume, and proportion of hypoxic areas within the target volume. Usually, the total dose of brachytherapy in H&N should be comparable to 50-70 Gy continuous LDR dose [47]. In the modern era, following the introduction of cross sectional image based volume optimized treatment planning, its limitations have become more and more evident. Nevertheless, we still need a system to describe and understand

Table 5. Representative results in intra-and perioperative brachytherapy (LDR/HDR/PDR)

Author	n	Anatomic site	BT dose (Gy)	LDR	HDR	PDR	5 years local control (%)	5 years OS (%)	Toxicity
Vikram <i>et al.</i> [107]	21	Neck, base of skull, orbit, pre-vertebral, peritracheal	48	¹⁹² Ir, wires	–	–	81 (2 yrs)	55 (2 yrs)	5% postoperative mortality 14% soft tissue necrosis
Nag <i>et al.</i> [112]	30	Ethmoidal cell, skull base, oropharynx	EBRT 40 BT 7.5-15	–	Single fx	–	67 Mean FU: 21 months	72 (CSR)	n.d.
Strege <i>et al.</i> [120]	18	Base of skull	10-30	–	Fx 2.5 bid	Office hours 5 × 2 Gy 2 h pulses	7 months PFS	n.d.	1/18 skin defect 1/18 osteomyelitis
Nutting <i>et al.</i> [132]	74	Neck	60	¹⁹² Ir, wires	–	–	23 WOF 66 WF	23	9% fistulation 8% wound breakdown
Teudt <i>et al.</i> [129]	35	Paranasal sinus	54	–	10-35	–	67	72 (3 yrs)	14% wound healing disturbances 17% sinus crusting 14% dysgeusia
Gaztanaga <i>et al.</i> [126]	97	Head and neck	32/40 = R0/R1 16/24 = R0/R1	–	IMBT bid	–	61.9 84.2	32.2 (DFS) 52.4 (DFS)	45.9% G3 (previous EBRT) 24.6% G3 (unirradiated)

LDR – low-dose-rate, HDR – high-dose-rate, PDR – pulsed-dose-rate, DFS – disease free survival, CSR – crude survival rate, WOF – without flap, WF – with flap, OS – overall survival, bid – twice a day fractions (min. 6 hours interval), IMBT – intensity modulated brachytherapy, fx – fraction

the relationship between applied inhomogeneous target dose and clinical outcome, as well the ability to compare treatment results of different reported experiences [167,168]. The Paris System geometry rules should be used as a pedestal to build a new system, where due to dedicated target dose inhomogeneities biological planning could be realized [13]. Since literature data regarding the relationship between IMBT dose inhomogeneity and late toxicities are rare in H&N cancer, the systematic collection and documentation of implant quality measures (COIN, DNR, etc.) for future evaluations are advisable [47].

Regarding applied doses/dose rates there are different reported experiences in the literature

Seed implants

The use of 80-200 Gy D_{90} values on the postimplant CT's was reported as feasible in H&N cancers if ¹²⁵I was

used as a permanent implant [107,108,156,169-171]. If molds are used, ¹²⁵I can be applied as a temporary implant. In this case, excellent outcome data were published with a mean dose of 55 Gy at 0.5 cm depth from the applicator surface [172]. In the case of ¹⁹⁸Au, the applied dose was similar, 50-55 Gy [173].

High-dose-rate brachytherapy

Unfavorable outcomes have been documented in patients treated with large single shot doses; however, dose painting can lower normal tissue toxicity [124]. In general, the use of fractionation in HDR brachytherapy is advisable. Excellent clinical results are presented with fraction doses of 2.5-6.0 Gy. It is possible to shorten the total treatment time by using two fractions daily, with a minimum of 6 hours between each fraction [26,47]. However, it seems to be advisable to keep the fraction dose low if the target volume is large.

Pulsed-dose-rate brachytherapy

All brachytherapy applications with more than two fractions per day are denoted as PDR. Depending on the daily number of fractions, two different types of fractionation can be followed: the daytime PDR (only during office hours) and continuous PDR (delivering fractions over 24 hours). In the interest of normal tissue preservation (keeping the dose rate low), PDR machines work with low initial activity (approx. 37.0 GBq) HDR sources. Following fractionation studies in animals [174,175], PDR treatments with longer pulse (fraction) intervals of up to 3 hours were proven to replace continuous LDR treatments [56]. The probability of local control and development of severe toxicities are in correlation with the irradiated volume, and with the dose maxima/dose inhomogeneity [176]. An analysis investigating the safety of "office time" versus 24 hour PDR applications found equality with both methods [177]. Regarding clinical outcome comparisons, there are no large cohort comparisons published in connection with H&N cancer.

Combined external beam therapy (+/- chemotherapy)

The combination of EBRT and/or chemotherapy (most frequently platinum based) with brachytherapy in the H&N is feasible [7,99,164,178]. Additional hyperthermia was proven as a modality improving radiotherapy treatment results in both brachytherapy and EBRT [47,179]; however, the method is not widely practiced. The use of IMBT as a boost complementary to EBRT can be performed in different ways: in combination with surgery as a "boost first" in the setting of perioperative IMBT or following the completed EBRT. The prolongation of total treatment time due to a long (> 14 days) time interval between IMBT boost dose and EBRT can negatively impact outcome results [180]. The usual IMBT boost dose varies between 10-20 Gy, complementary to 45-60 Gy EBRT dose [13,47].

Conclusions

Technical developments and multidisciplinary teamwork lead to better understanding of the role of IMBT in H&N cancer treatments and its place in up-to-date treatment regimes. Since surgery has also developed in the past decades, there has been a change in the role of IMBT: instead of focusing on the cure of small tumors. The current focus is on local dose escalation complementary to EBRT, function preservation through perioperative applications, and successful treatment of recurrent disease. However, to offer the full benefits to patients, IMBT in H&N cancer needs to be performed by experienced (multidisciplinary) teams in dedicated centres with a high workload in the field.

Disclosure

Author reports no conflict of interest.

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