Mini-Review

Intraoperative radiotherapy (IORT) in the treatment of head and neck cancer

Marc W. Münter[1], Ulrich Köppen[1], Anika Ramuscak[2], Christian Sittel[2], Nils Wegner[1]

[1]Department of Radiation Oncology, [2]Department of Otorhinolaryngology-Head and Neck Surgery, Klinikum Stuttgart, 70174 Stuttgart, Germany
Correspondence to: Prof. Dr. med. Marc W. Münter. Department of Radiation Oncology, Klinikum Stuttgart, Kriegsbergstr. 60, 70174 Stuttgart, Germany. Email: m.muenter@klinikum-stuttgart.de.

Abstract: This review will focus on the clinical results of intraoperative radiotherapy (IORT) in head and neck cancer (HNC). Treatment in different clinical situations of HNC is challenging and requires a multidisciplinary team to also minimize side effects of curative disease management which often reduce the quality of life of the patients. Even though early and more advanced stages can be treated with curative intent in many HNC cases, local recurrences still pose a clinical problem. Radiotherapy is required in the primary treatment, in adjuvant situations and also for recurrent disease. IORT offers the theoretical and practical option to apply radiation in close discussion with the surgeon and with high local precision to areas of tumor involvement and/or surgical resection. Protection of normal tissue is an important aspect of radiation therapy, especially when a second treatment course of radiation is planned or necessary. In such instances IORT can offer additional benefit for patients with HNC when compared with external beam radiotherapy (EBRT).

Keywords: Head and neck cancer (HNC); radiotherapy; intraoperative radiotherapy (IORT); review

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Introduction

Head and neck cancers (HNCs) represent malignancies arising in the lip, oral cavity, pharynx, larynx and paranasal sinus. These tumors often require comprehensive and complex treatment regimes. Normally stage, pathologic findings, the specific site of the tumor and the clinical situation of the patient guide the treatment. Early stage tumors could be dealt with in curative intent in most cases. Apart from a surgical approach also conservative treatment modalities can be offered to the patient. Surgical and non surgical treatment modalities result in similar survival rates in these individuals. Favourable clinical situations account for approximately 30% to 40% of the cases. For patients with locally or regionally advanced situations combined modality therapy is generally recommended. In general a surgical approach followed by an adjuvant radio- or radiochemotherapy is then to be employed. Alternatively these patients can primarily be treated by a combination of radiotherapy and chemotherapy. External beam radiotherapy (EBRT) is by far the most common conservative treatment option. Curative treatment approaches make use of modern techniques like intensity modulated radiotherapy (IMRT) in combination with image-guided radiotherapy (IGRT). These techniques offer the opportunity to increase the dose to the tumor at the same improving the sparing of surrounding normal tissue and organs. IMRT in particular assists the protection of the salivary glands and thus reduces xerostomia, which is a frequent side effect after radiotherapy with conventional treatment techniques.

In primary curative treatment special modalities like brachytherapy and intraoperative radiotherapy (IORT) are rarely used. In other clinical situations such as tumor recurrence or advanced disease a second course of radiation therapy may be required. In the majority of such situations the application of high doses in second courses is limited due to the tolerance doses of normal tissue. Modern techniques like IMRT or special forms of radiotherapy like brachytherapy or IORT might help to overcome this problem. For HNC brachytherapy with high dose rate (HDR) normally using iridium 192 sources is commonly used. Intraoperatively flexible multichannel surface applicators are

placed into the treatment field and HDR-brachytherapy is applied in the operating theatre. HDR-brachytherapy is a fairly widely employed IORT approach for HNC.

For the majority of surgical indications in oncology, however, linear accelerator based IORT using high-energy electrons (IOERT) or one system deploying low energy photons is present standard of care. This review will therefore mainly focus on linac based IORT techniques. Currently only a small numbers of publications cover this challenging issue.

The main mechanism of IORT is tumor cell kill by means of one high dose fraction. IORT has therefore the potential to improve local control and the therapeutic ratio in many tumors. One major advantage is the reduction of the treatment volume through direct visualization of the tumor or its bed. Furthermore, direct shielding, operative mobilization or the use of different beam energies can exclude dose limiting normal structures.

Linac-based IORT for recurrent HNC

The treatment algorithm of recurrent HNC is rather problematic. In many cases patients have previously received multimodal treatment including primary or adjuvant radiotherapy, mostly so in combination with chemotherapy. Therefore the choice of individual radiotherapy at the time of recurrence is limited due to earlier treatment(s) of the patient. Resectable tumors will be operated on. Yet surgery alone in heavily pretreated tissue is often incapable of completely removing larger size tumors with possible vessel and/or cervical nerve infiltration, thus necessitating additional methods to ensure prolonged curative or palliative effects.

Schleicher *et al.* published (1) a study of 113 intraoperative irradiations in a total of 84 preirradiated patients with a standard dose of 20 Gy using high-energy electrons. The recurrent tumors were mainly localized in the oro-/hypopharynx and larynx regions. IOERT did not result in excessive complication rates compared to surgery alone. In 88% of the symptomatic patients a good palliation of the symptoms were achieved using a combination of surgery and IOERT. Median survival was 6.8 months in this study. The University of California/San Francisco study included 137 patients with recurrent HNC (2). Here IOERT was given after tumor resection applying a median dose of 15 Gy and 83% of the patients received additional EBRT. Median survival was 12 months for patients with neck recurrence versus 20 months for patients treated for recurrence at the primary site. Two year survival was 52%. In-field control at one and two years was found to be 76% and 69%, respectively. Chen *et al.* (2) reported only three cases with serious toxicities (facial pain, wound dehiscence and trismus).

The Memorial Sloan Kettering Cancer Center presented 34 patients with recurrent HNC after EBRT receiving a median IORT dose of 15 Gy. Perry *et al.* (3) reported severe complications only in a minority of patients and a median overall survival of 24 months. Apparently superior survival in patients in whom disease was locally controlled could be achieved. In-field control at one and two years was found to be 66% and 56%, respectively. Other HDR IORT data came from Scala *et al.* (4). A total of 76 patients with recurrent HNC were reported and treated between 2001 and 2010 with HDR IORT. Dose was typically prescribed at 0.5 cm depth from the surface of the applicator. A dose of 12 Gy was applied for patients with negative margins, and between 15 and 17.5 Gy for patients with positive margins. No increased side effects have been reported in this study. The authors found significantly longer survival rates for patients achieving in-field control versus patients with in-field progression, with 33 versus 17 months, respectively. Median overall survival was 19 months with 42% of the patients surviving at least two years. After two years the estimated in-field tumor control was 62%.

A publication from the Mayo Clinic reported results of IOERT for recurrent skull base cancer previously treated by combined therapies (5). Results from 34 patients with squamous cell carcinoma (SCCA) and 10 patients with nonSCCA were presented. IOERT doses between 12.5 to 22.5 Gy were applied. The only complication directly associated with the IOERT treatment was a neuropathy in a patient received a dose of 22.5 Gy. For the SCCA group the tumor control rate at two years were 46% and 52% for the nonSCCA patients. At two years overall survival and disease-free survival was 50% and 40%respectively for the nonSCCA patients, and 32% and 21% respectively for the SCCA group.

Linac-based IORT in the primary treatment of HNC

Several single institution series have examined the use of IORT in different concept of a primary treatment setting with respect to cancer control and toxicity. The clinical results of these studies are inhomogeneous and represent only retrospective data. Therefore no general treatment recommendation concerning IOERT can be given.

Marucci *et al.* (6) delivered the IOERT treatment as an "early boost" in patients with locally advanced HNC. A total of 25 patients were enrolled in this study. All patients underwent radical surgery and 17 had microvascular flap reconstruction. Patients received in all cases a dose of 12 Gy by with electrons of varying high energies in the operating room. Twenty patients received adjuvant EBRT with a dose of 50 Gy. Different locations of tumors were treated in this

feasibility study. The authors concluded that IOERT is safe and feasible as an "early boost". During the follow-up no patient death was related to the radiation treatment. The 2-year overall survival in this study was 64.5%; loco regional relapse free survival was 58.5% and disease free survival was 50.6%. Zeidan *et al*. (7) published the experience of IOERT for advanced cervical metastases either in untreated patients or in a salvage setting. A total of 231 patients were treated and doses between 10 and 25 Gy for IOERT were prescribed. Doses of 15 and 20 Gy were mainly applied. In 50 patients postoperative EBRT with a median dose of 45 Gy was given. A total of 81.4% of the patients received radiotherapy as a primary treatment. In general only large or bulky disease cervical metastases, in which a dissection with obviously clean margins or suspected residual microscopic disease appeared to be not possible, were included. Most *et al*. (8) reviewed the data of their institutions concerning IORT and flap reconstruction after resection. Twenty-five operations with flaps were performed in 21 patients in an IOERT setting. Patients received between 10 and 15 Gy. Wound revision was necessary in three cases and required a second surgical intervention. No perioperative mortalities were caused by IOERT. Therefore the authors concluded that reconstructions using flaps in combination with IOERT can be achieved with undisturbed wound healing in most of the patients. A polish group performed IORT as a boost in patients with early stage oral cancer. Rutkowski *et al*. (9) evaluated a low energy photon system (INTRABEAM®; Carl Zeiss Meditec AG) in 16 patients with tumor of the mobile tongue or floor of the mouth. The system can generate low energy X-rays with 30-50 kV and therapy will be preformed in the operating room. Mean treatment time for IORT in this study was 15.5 min (range: 9.75-19.42 min). Different applicator sizes between 1.5 to 5 cm were utilized and a radiation dose of 5, 7 or 7.5 Gy specified at the reference point at a distance of 5 mm of the surface of the applicator was applied according to the margins and the tumor volume. In all cases EBRT was performed to a total dose of at least 50 Gy. The authors reported on a median follow-up of 36 months. IORT with low energy photons did not increase acute mucosal reaction. In all patients a complete disappearance of acute mucosal reactions could be observed within a median time of 35 days after completing the treatment courses. Thereafter no subjective symptoms or further late side effects were reported. In three patients nodal lymph node recurrence was detected. One patient died due progression of disease, and two patients were controlled after salvage therapy. Distant metastases developed in two patients who both died in the wake of progressive disease.

A very interesting publication established IOERT in the primary treatment of parotid cancer (10). Tumors of the salivary glands are normally dealt with by surgical resection and adjuvant radiotherapy. Despite combined treatment modalities advanced tumors frequently show high rates of local recurrence. In general, salivary gland tumors are relatively radio resistant and thus require also high dose radiotherapy, also in the adjuvant clinical approach. Zeidan *et al*. (10) presented a retrospective study of 96 patients with parotid tumors treated with IOERT primarily or for recurrent disease. Previous EBRT was performed in 33 patients with a median dose of 60 Gy. The median interval between previous EBRT and IOERT was 8.7 months. Fifty were treated with primary surgery and 46 with salvage surgery. Electron energies between 4 and 6 MeV were used and doses of either 15 or 20 Gy were applied. In 55 patients additionally postoperative radiotherapy was prescribed. The recurrence free survival rate at 1, 3 and 5 years was 82%, 68.5% and 65.2%, respectively. One patient experienced local recurrence, 19 developed regional recurrence and 12 distant metastases. After 1, 3 and 5 years the overall survival rate after surgery and IOERT was 88.4%, 66.1% and 56.2%. Complications occurred in 27% of the patients. Seven had postoperative vascular complications, 6 developed trismus, 4 suffered from osteoradionecrosis, 4 had fistulas, flap necrosis was seen in 2 patients, wound dehiscence also in 2 patients, and 1 developed a neuropathic disorder. The authors concluded that the promising results of this retrospective study support the initiation of a prospective phase III trial.

One very interesting publication focused on the treatment of locally advanced esophageal and gastroesophageal junction carcinoma with IOERT. Even normally not grouped with head and neck tumors, esophageal cancer has a comparable origin, risk factors and treatment approaches. Calvo *et al*. (11) published a concept in which patients received preoperative chemoradiation followed by surgery with or without an IOERT boost. A total of 53 patients with primary esophageal or esophagogastric cancer were included in this prospective study. A total of 37 patients received an IOERT boost of the tumor bed prior to anastomotic reconstruction in the mediastinum and upper abdominal lymph node area. Postoperative mortality and perioperative complications for the whole treatment group amounted to 11% (n=6) and 30% (n=16). All cases of postoperative mortality occurred in the IOERT group, however without statistical significance (P=0.087). Concerning the overall postoperative complications no difference was found (approximate 30% in both treatment arms). With a median follow-up of 27.9 months five year overall survival and disease free survival was 48% and 36%, respectively. In a univariate analysis it was

found that IOERT was associated with a significant lower risk of loco regional recurrence (P=0.004). The same holds true for the multivariate analysis where local recurrence was significantly less in the IOERT arm (P=0.01).

Conclusions

Different techniques of IORT can be used for the treatment of HNC, such as HDR-brachytherapy, IOERT or IORT with low energy photons. Scientific evidence is poor so far for IORT with regard to this clinical indication. Nevertheless, promising results were achieved over the last decades by centers specialized in the treatment of HNC with IORT. Until now, however, no randomized study has been performed. Therefore IORT might be a good option in patients with recurrent disease after previous primary radiotherapy. It is well known that the treatment of locally recurrent HNC poses a therapeutic challenge. In curative treatment therefore every therapeutic option should be made use of to improve the outcome of the patient. Smaller and more advanced IORT units in the operating room might help to propagate broader use of this promising therapeutic method.

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