

## **INTRAOPERATIVE RADIATION THERAPY AS AN “EARLY BOOST” IN LOCALLY ADVANCED HEAD AND NECK CANCER: PRELIMINARY RESULTS OF A FEASIBILITY STUDY**

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**Abstract:** *Background.* The acute toxicity of intraoperative radiation therapy (IORT) delivered as an “early boost” after tumor resection in patients with locally advanced head and neck cancer was evaluated.

*Methods.* Twenty-five patients were enrolled in the study. All patients underwent surgery with radical intent, and 17 had microvascular flap reconstruction. The IORT was delivered in the operating room. Twenty patients received adjuvant external beam radiation therapy (EBRT).

*Results.* Five patients experienced various degrees of complications in the postoperative period, all of which were treated conservatively. One patient had a partial flap necrosis after EBRT that was treated with flap removal. Six deaths were recorded during the mean follow-up period of 8 months; none of the deaths were related to radiation treatment.

*Conclusion.* This feasibility study shows that the use of IORT as an early boost is feasible with no increase in acute toxicity directly attributable to radiation. ©2008 Wiley Periodicals, Inc. *Head Neck* 30: 701–708, 2008

**Keywords:** intraoperative radiation therapy; toxicity; locally advanced cancer; head and neck cancer; electron beam

**P**atients with stage III and IV head and neck cancer have a low probability of cure. Only 30% to 40% of those treated with surgery and adjuvant therapy are free of disease at 5 years, and the majority of those who do not survive have a locoregional relapse.<sup>1,2</sup>

Risk factors for locoregional recurrence include positive resection margins; nodal metastasis with extracapsular extension (ECE); clinical advanced T or N classification; perineural or lymphovascular invasion and invasion of surrounding neck structures such as the carotid artery, skin, and base of the skull.<sup>1</sup> To reduce the clinical impact of such risk factors, higher doses of external beam radiation therapy (EBRT) are needed, as demonstrated in a phase II randomized study evaluating dose escalation of postoperative EBRT for patients with head and neck cancer.<sup>3</sup>

One current approach for treating locally advanced tumors of the head and neck is the use of concurrent chemoradiotherapy in the postoperative setting. Two randomized studies have been conducted by the European Organization for Research and Treatment of Cancer and the Radiation Therapy Oncology Group, and both have

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shown an increased locoregional control when chemotherapy is added to radiation, but at the expense of increased toxicity.<sup>4,5</sup> A multi-institutional study has evaluated the influence of shortening the treatment duration from the end of the surgery to the end of radiation. In high-risk patients, there was a significant increase in locoregional control and survival in patients treated in less than 11 weeks when compared with those treated in more than 11 weeks.<sup>6</sup>

In an effort to further improve postoperative treatment of high-risk patients, intraoperative radiation therapy (IORT) offers an alternative approach. Delivery of an early radiation dose to the tumor bed allows a reduction in the total treatment time without increasing toxicity. IORT is defined as the delivery of a single large dose of radiation at the time of surgery when the tumor bed is exposed, and the normal adjacent structures can be retracted or shielded. This technique offers a number of theoretical advantages: (1) decreased possibility of geographical miss as the radiation is delivered at the time of surgery when the tumor bed is exposed and can be easily identified, (2) increased possibility of sparing normal surrounding tissue, (3) increased probability of the sterilization of all stem cells, as radiation is administered when the tumor cell number is at its minimum, (4) increased biological efficacy per unit dose due, in part, to the administration of radiation as a single fraction with no time elapsing between fractions, (5) decreased dose of EBRT, (6) decreased overall treatment time reducing tumor cell repopulation during treatment, which is particularly important in head and neck tumors.

The purpose of this study was to test the feasibility of IORT as an early boost in resectable locally advanced head and neck cancer treated with surgery and adjuvant radiation.

## MATERIALS AND METHODS

The accrual of patients in the protocol started in January 2004.

The inclusion criteria were patients with resectable locally advanced head and neck cancer; primary or recurrent neoplasms, including skin cancer; age of more than 18 years; no previous irradiation; and a signed consent form.

Before surgery, all patients underwent clinical examination under anesthesia with tumor biopsy; CT or MRI of the primary and the cervical nodes; thoracic CT scans; and neck and liver ultrasonography.

**Table 1.** Site of primary tumors.

Site of primary tumors	No. of patients
Oral cavity	11
Oropharynx	1
Hypopharynx	2
Larynx	2
Parotid	1
Skin	6
Unknown primary	2

Twenty-four patients had squamous cell carcinoma and 1 had salivary gland ductal carcinoma of the parotid. Seventeen patients had clinical stage IV disease; 8 had recurrent disease after surgical resection (6 skin, 1 oral cavity, and 1 larynx). The primary sites involved were oral cavity, oropharynx, hypopharynx, larynx, unknown primary, parotid gland, and skin (Table 1).

Pulmonary and cardiac function tests and anesthesiological examination were performed, and the patients were classified according to the American Society of Anesthesiologists (ASA) scale (ASA I = 2, ASA II = 15, ASA III = 5, ASA IV = 3; Table 2)<sup>7,8</sup> to categorize the gravity of their comorbid disease. Thirty-two percent of the patients had a variety of preexisting conditions as well as comorbid disease, and 40% had a history of tobacco and/or alcohol abuse. Patients performance status was  $\leq 2$  according to the World Health Organisation (Zubrod) Scale. IORT was delivered after complete tumor resection (R0), assessed by intraoperative pathologic examination of frozen section margins. The margin status was then confirmed by the definitive pathologic report. Seventeen patients had reconstructive surgery with microvascular free-tissue transfer or myocutaneous pedicled flap (Table 2).

IORT was delivered in the operating room using Novac7 (Hitesys, Aprilia, Italy; see Figure 1); a dedicated movable electron beam linear accelerator with a nominal energy of 3, 5, 7, and 9 MeV.

Novac7 is equipped with 3 sets of Plexiglas applicators of different diameters, ranging from 4 to 10 cm. The dose-rate used for treatment varied between 6 and 26 Gy/min depending on the energy and applicator's diameter. The energy and collimator diameter for each patient were chosen by the IORT team on the basis of the tumor extension. The team was composed of a surgeon, a radiation oncologist, and a physicist. Seven MeV was used in 22 patients and 9 MeV in 3. The maximum and 90% isodose depths were 12 and

**Table 2.** Primary tumor site, ASA classification, surgical procedures, and pathological classification.

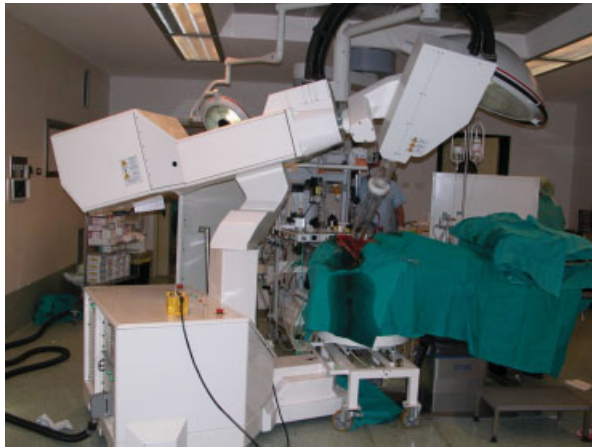
No.	Tumor site	ASA	Surgical procedures	pTN
1	Hypopharynx	III	Hemipharyngolaryngectomy + bilateral MRND	T3N2b
2	Larynx-peristomal recurrence	II	Bilateral MRND + bilateral VI levels	rT4aN0
3	Unknown	II	RND	TxN3
4	Hypopharynx	II	Total-pharyngolaryngectomy + RND + pectoralis major pedicle flap	T3N3
5	Oral cavity	III	Subtotal glossectomy + bilateral RND + forearm free flap	T2N2c
6	Oral cavity	I	Composite resection + bilateral MRND + osteocutaneous fibula free flap	T4aN2b
7	Oral cavity	II	Pull-trough subtotal glossectomy + bilateral MRND + pectoralis major pedicle flap	T2N0
8	Skin	IV	RND extended to parotidectomy + skin + mastoidectomy + pectoralis major pedicle flap	T4N1
9	Oral cavity	II	Transmandibular subtotal glossectomy + rim mandibulectomy + bilateral MRND + recuts abdominis free flap	T2N0
10	Oral cavity	II	Composite resection + MRND + osteocutaneous fibula free flap	T2N2c
11	Skin	III	RND extended to skin (sparing JV) + parotidectomy + pectoralis major pedicle flap	rTON1
12	Oral cavity	IV	Composite resection + bilateral MRND + pectoralis major pedicle flap	T3N2b
13	Oral cavity	II	MRND	rN2b
14	Oral cavity	III	Composite resection + bilateral MRND + pectoralis major pedicle flap	T4aN1
15	Oral cavity	II	Composite resection + MRND + osteocutaneous fibula free flap + forearm free flap	T4aN2c
16	Skin	II	Total parotidectomy extended to skin + RND + forearm free flap	rT4N1
17	Oropharynx	II	RND extended to the skin	N2b
18	Skin	II	Subtotal petrosectomy extended to external ear + RND + parotidectomy + temporalis muscle flap	rT2N0
19	Parotid	I	Total parotidectomy + MRND	T3N2b
20	Skin	II	Subtotal petrosectomy extended to external ear + RND + parotidectomy + pectoralis major pedicle flap.	rT2N0
21	Larynx	IV	Total laryngectomy extended to thyroid gland and strip muscles	T4aN0
22	Oral cavity	III	Composite resection + bilateral MRND pectoralis major pedicle flap	rT4aN2b
23	Skin	II	RND extended to external ear, parotid and ear canal + pectoralis major pedicle flap	rTON1
24	Unknown	II	RND	TxN2b
25	Oral cavity	II	Composite resection + bilateral MRND + osteocutaneous fibula free flap + recuts abdominis free flap	T4aN0

Abbreviations: ASA, American Society of Anesthesiologists classification; RND, radical neck dissection; MRND, modified radical neck dissection; JV, jugular vein.

17 mm for 7 MeV, and 15 and 20 mm for 9-MeV energy beams, respectively. The collimator mean diameter was 6 cm (range, 4–8 cm). The dose delivered was 12 Gy in all patients. The biologically equivalent dose of 12 Gy administered as a single dose is approximately 19 Gy administered at 2 Gy/fraction, based on an  $\alpha/\beta$  ratio of 15 Gy.<sup>9</sup> The dose was prescribed at the 90% isodose. The accuracy of the actual delivered dose was checked using in vivo dosimetry. The micromosfet dosimeter was chosen, because its small size (active area, 0.2 mm  $\times$  0.2 mm) reduces or eliminates field perturbation. The dosimeter, placed

inside a sterile catheter, was positioned in the center of the IORT field to measure the entrance dose online.

The mean time of surgical interruption was 20 minutes (range, 15–30 minutes). IORT was administered to the primary tumor bed in 17 patients, to the nodal tumor bed in 4 patients (Figure 2), and to the primary and nodal tumor bed which were included within the same field in 4 patients (Table 3). The pathology reports confirmed the clinical staging in 23 patients and downstaged 2 of them (8%) from clinical stage IV to pathologic stage II (Table 2).



**FIGURE 1.** Movable dedicated linear accelerator. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

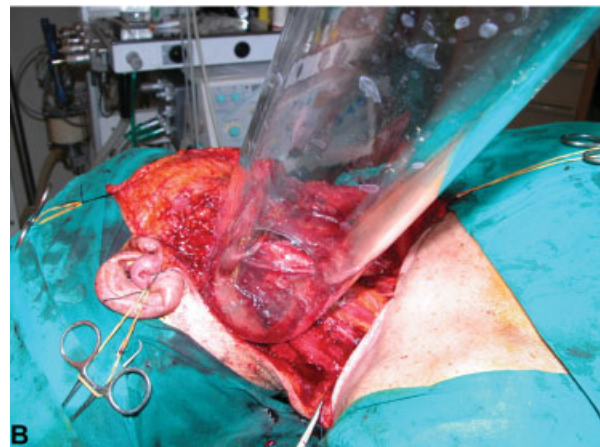
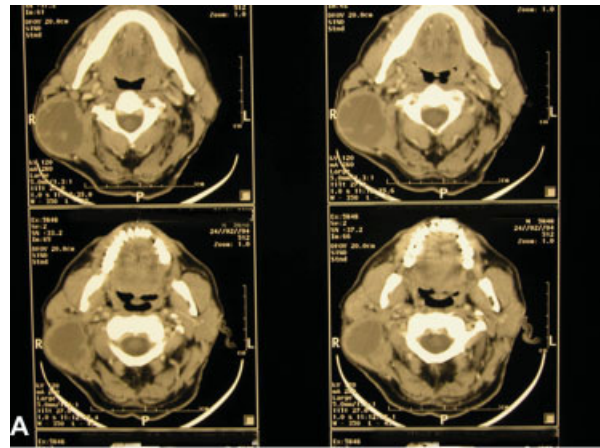
Twenty patients also received adjuvant EBRT of 50 Gy in 5 weeks; and 4 patients, with postoperative good performance status and lymph nodes with ECE in the pathology report, received concomitant chemotherapy. Five patients did not receive adjuvant therapy: 1 patient because of pathologic downstaging that did not require further treatment; 2 patients because of poor postoperative performance status; 1 patient because of the discovery of a second primary tumor, whose treatment got priority; and 1 patient who refused.

## RESULTS

From January 2004 to January 2006, 25 patients (20 men and 5 women) were enrolled in the feasibility study on the use of IORT as an early boost. The mean age was 64 years, with a range of 36 to 78 years.

All patients were evaluated every month after the end of treatment, and all complications were recorded. Five patients experienced various degrees of complications in the immediate postoperative period, and 1 patient experienced complications after the completion of adjuvant EBRT (Table 4). One patient had a hematoma on the first postoperative day, which was successfully treated with surgical revision of the wound. The patient experienced no more complications.

Three patients experienced fistula formation. Following hemipharyngolaryngectomy and bilateral modified radical neck dissection (RND) for a pT3N2b carcinoma of the hypopharynx, 1 patient developed a pharyngocutaneous fistula on the fifth



**FIGURE 2.** (A) CT scan showing an enlarged lymph node; (B) intraoperative radiation therapy collimator position after nodal resection. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

postoperative day. The patient was treated with a compressive dressing and prolonged nasogastric feeding tube until complete closure of the fistula. The second patient had undergone a composite

**Table 3.** IORT sites.

Primary tumor site	IORT site		
	T	N	T+N
Oral cavity	9	1	1
Oropharynx		1	
Hypopharynx			2
Larynx	2		
Parotid	1		
Skin	5		1
Unknown primary		2	

Abbreviations: IORT, intraoperative radiation therapy; T, primary tumor, N, neck; T+N, primary tumor and neck.

**Table 4.** IORT complications.

Type of complication	No. of patients
Hemathoma	1
Fistula	2
Fistula with partial flap necrosis	1
Partial flap necrosis with wound dehiscence	1
Flap necrosis with underlying bone necrosis	1

Abbreviation: IORT, intraoperative radiation therapy.

resection, bilateral modified RND, and pectoralis major pedicle flap for a pT4aN1 tumor of the retromolar trigone. The orocutaneous fistula was treated and resolved with compressive dressing and antibiotic therapy. The third patient had undergone a composite resection, bilateral modified RND, and pectoralis major pedicled flap reconstruction for a recurrent pT4aN2b tumor of the floor of the mouth. The patient developed partial flap necrosis and orocutaneous fistula, which were treated with wound curettage and compressive dressing, until complete resolution. The fifth patient developed a partial flap necrosis with wound dehiscence after the excision of a recurrent cutaneous cancer. The patient was treated by removal of the ear, including the external ear canal and the parotid gland RND and pectoralis major pedicle flap reconstruction. The wound was treated with local dressing until complete resolution.

One patient developed a major delayed complication. He had undergone a composite resection, bilateral modified RND, and osteocutaneous fibula free-flap reconstruction for a pT4aN2b tumor of the retromolar trigone. About 2 weeks after the end of postoperative radiation therapy, the patient developed skin and bone flap necrosis. The patient was treated with surgical removal of the flap and reconstruction.

The mean and median time interval between the surgery and the beginning of the radiotherapy was 60.5 and 60 days (range, 32–90 days). The mean and median time for the completion of the entire treatment from the surgery to the end of the radiotherapy or chemoradiotherapy was 99.5 and 92 days (range, 83–146 days).

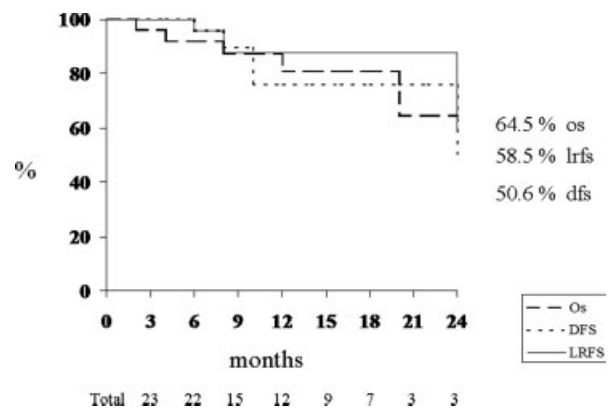
With a mean and median follow-up calculated from the completion of the therapy of 10 and 9 months (range, 3–25), 17 patients are alive and without evidence of disease, and 2 are alive with systemic disease. One patient, treated for a recurrent skin cancer, developed a local recurrence outside the IORT field 3 months after treatment and

was treated again with surgery and a second IORT. The patient is now alive with no evidence of local disease, but had developed a single lung metastasis at 6 months after the second surgery and was treated with resection and adjuvant chemotherapy. Six patients have died. Two, classified as ASA III and IV, died in the postoperative period due to deteriorating general condition, 1 died of respiratory infection 7 months after surgery, 1 died of systemic progression at 15 months, and 1 died of locoregional recurrence at 21 months. One patient, treated with IORT on the neck after RND for a tumor of the tonsil pN2b with ECE, developed an in-field relapse on the dissected neck 6 months after surgery and died 2 months later from carotid blow-out. In conclusion, at the last follow-up, 2 patients, that had received IORT and EBRT, had in-field relapse and died of locoregional progression.

The 2-year overall survival was 64.5%; locoregional relapse-free survival was 58.5%, and disease-free survival was 50.6% (see Figure 3). The data were calculated accurately using the Kaplan–Meier method.

## DISCUSSION

The treatment of locally advanced cancer of the head and neck poses a challenge for the surgeon and the radiation oncologist because of the high incidence of locoregional recurrence. In an attempt to improve locoregional control, both the surgeons and the radiation oncologists have tried to optimize their approaches. Surgical interventions are more extensive due to the success of reconstructive surgery. But such approaches are not without complications that can result in flap removal, especially in advanced cases. For



**FIGURE 3.** Survival curves. Os, overall survival; DFS, disease-free survival; LRFS, locoregional-free survival.

**Table 5.** IORT in head and neck cancer: past experiences.

	Year	No. of patients	Median FU, mo	Dose, Gy	Gross residual, %	Previous EBRT, %	Complication, %	LRF, %
Garrett et al <sup>17</sup>	82–84	28	14	10–100	23	61	10,3*	34
Toita et al <sup>22</sup>	88–92	25	19 (24 min in 35 pts.)	10–30	23	33	22*	46 (all in-field <sup>†</sup> )
Freeman et al <sup>16</sup>	82–88	104	24	15–20	20	42	14,4 (8,6*)	60 <sup>‡</sup>
Rate et al <sup>20</sup>	82–89	47	14	15–25	13	100	12,7 (6,3*)	38
Coleman et al <sup>15</sup>	91–95	46	20	14–18	2	72	24	39
Martinez-Monge et al <sup>18</sup>	84–95	31	N/A	10–15	50	47	22,5	67
Spaeth et al <sup>21</sup>	89–94	95	11	10–40	72	95	28,4	89
Nag et al <sup>19</sup>	92–97	38	30	15–20	8	100	16	79 (66 in-field <sup>†</sup> )
Chen et al <sup>23</sup>	91–04	137	41	10–18	0	83	6,5	49

Abbreviations: IORT, intraoperative radiation therapy; FU, follow-up; EBRT, external beam radiation therapy; LRF, locoregional failure; N/A, not available.

<sup>†</sup>Within the IORT field.

\*Only major complications (carotid blowout or osteonecrosis).

<sup>‡</sup>Calculated on 35 patients with a minimum of 24-mo follow-up.

example, Wei et al<sup>10</sup> reported an overall success rate of 97% in more than 600 single microvascular flap reconstructions. This success percentage goes down to 90.9% when 2 flaps were used for the reconstruction following more extensive resections.<sup>11</sup> Such data are similar to those obtained in our small series in which only 1/17 reconstructive surgeries needed a second surgery with flap removal. Similarly, the rate of complication is in the range of those reported in other large series. Vartanian et al<sup>12</sup> found a 36.1% complication rate in 437 patients after reconstructive surgery with myofascial/myocutaneous flaps. Singh et al<sup>13</sup> found a 28% complication rate in 200 microvascular free tissue transfers, and an advanced Charlson comorbidity grade was associated with an increased risk for the development of complication. Unpublished data derived from a review of the complication rate of 112 microvascular free-flap reconstructions performed at our institute (excluding those included in this study) found a complication rate of 27%. These data are in agreement with those found in the literature and similar to those reported for the patients enrolled in the present study. Surgical approaches without reconstruction, such as total laryngectomy, are not without side effects. Pharyngocutaneous fistulas after total laryngectomy remains a complication, in which predisposing factors are not yet clearly identified. Its incidence can be as high as 16% as recently reported by Galli et al<sup>14</sup> in a series of 268 patients undergoing total laryngectomy.

Thirty-two percent of the patients included in the present study were affected by serious comorbidity and 40% were heavy drinkers (7–9 drinks or beers or glasses of wine per day) and/or smokers. These patients all underwent complex exci-

sion and reconstructive surgery, and none of the complications were directly attributable to the IORT. The overall 20% (5/25) complication rate, and in particular the 23% rate (4/17) after flap reconstructive surgery, can be considered in the normal range.

Radiation oncologists have tried to increase locoregional control by increasing the total dose or shortening the overall treatment time by increasing the dose per fraction or the number of fractions delivered daily. And again, gains in tumor response were accompanied by increased acute toxicity<sup>6</sup> that is not always well tolerated by patients with significant comorbid disease, after an extensive reconstructive surgery.

Because of the more limited exposure of normal tissues, IORT can be used to increase the dose of radiation to the target area without increasing the side effects, and therefore offers a promising procedure for the treatment of locally advanced head and neck tumors.

IORT has been known for 40 years and has been used in different tumor sites. However, its use has been very limited, largely due to the difficulty of transporting patients, in the middle of the surgical procedure, from the operation room to the radiation treatment room, which is commonly quite far away. The introduction of a dedicated linear accelerator in the operating room has made IORT a much simpler and feasible treatment that causes only a brief interruption of surgery and has renewed the interest in the approach.

The major experiences in the use of IORT in head and neck cancer were published in the 1980s and 1990s,<sup>15–22</sup> with the exception of a more recent publication by Chen et al<sup>23</sup> (Table 5). The number of

patients between and within each reported study is limited and very heterogeneous. In particular, within the same study, patients with advanced primary or recurrent tumor after irradiation were included; the IORT doses varied from patient to patient, and surgical resection margins were not always negative. Such variability of inclusion criteria makes an evaluation of the real value of IORT in terms of locoregional control and toxicity very difficult.

Nevertheless, some useful information can be derived from those experiences. One is that it is important to distinguish between primary advanced versus recurrent disease after surgery and advanced and recurrent tumors after radiation. In fact, in the experience of Martinez-Monge et al,<sup>18</sup> the inability of delivering further EBRT after previous radical irradiation increased the locoregional relapse to 79%. Other important information, as the authors pointed out in the same paper, is that in patients with gross residual disease, IORT, even with a dose of 20 Gy, was not enough to ensure local control, but useful only as palliation.<sup>18</sup> Similar results were also reported by Chen et al.<sup>23</sup> These authors found positive microscopic margins to be the only parameter predictive of in-field recurrence. Additional important information reported in these studies, and in particular in the UCSF experience with the largest series of 137 patients,<sup>23</sup> is that IORT related toxicity was minimal when IORT doses were 15 Gy or less. The major side effects were carotid blowout and osteoradionecrosis, which occurred only for doses of 20 Gy or higher at a time ranging from 1 to 21 months for carotid blowout<sup>22</sup> and from 3 to 29 months for osteoradionecrosis.<sup>15-17,20,22,24</sup>

Starting from this information, we defined the inclusion criteria in this study. First, we limited the accrual to patient with advanced or relapsed disease that had not received prior EBRT. The IORT was not the exclusive irradiation treatment but was employed only as a boost for standard postoperative EBRT. The EBRT dose was 50 Gy. Second, IORT was delivered only after the pathologist confirmed negative margins. And third, the dose was limited to 12 Gy.

It is difficult to compare the complication rate after surgery and IORT in this study, with data reported in the literature. A number of factors, not always described in the manuscripts, influence the complication rate, ie, the extension of the disease and consequently of the resection, the need and type of reconstructive surgery, the patients' general condition before the resection, and the presence of serious comorbid disease.

The purpose of the present study was not to evaluate local control considering the small number of cases and the short follow-up, but the fact that there were only 2 in-field local relapses at 6 and 19 months seem encouraging. Previous publications have emphasized the importance of a short treatment time from surgery to the completion of postoperative radiotherapy. Ang et al<sup>6</sup> reported that completing the therapy in more than 13 weeks yielded a lower local control rate. Rosenthal et al<sup>25</sup> showed that a total treatment time of <100 days is associated with improved tumor control and survival. In our study, despite the long healing and recovery time needed after the complex reconstructive surgeries, the median time for the completion of the entire treatment was 92 days, because of the reduced time for EBRT. In addition, the "early boost" IORT dose delivered immediately after tumor resection on the tumor bed would be expected to sterilize a substantial number of tumor clonogens, possibly increasing the surviving tumor cells' doubling time, and consequently decreasing the negative impact of a long interval between surgery and radiation. The data reported are the result of a prospective feasibility study in which the limits are due to the heterogeneity of the patients accrued in the study. The enrolled patients were seen with very different lesions that required various types of surgical approaches and with very different intrinsic risk of postoperative complication and a substantial degree of complexity of IORT delivery.

## CONCLUSION

This study on the use of IORT as an early boost in locally advanced resectable head and neck cancer shows that such an approach is feasible with no increase in acute toxicity directly attributable to the irradiation. Interruption and prolongation of the surgical procedure was minimal due to a dedicated movable linear accelerator in the surgical suite. This study cannot assess the oncological efficacy of the procedure because of the small number of patients and short follow-up, but the result of only 2 in-field relapses seem encouraging. Further studies are needed to evaluate the efficacy of such an approach for different primary lesions, surgical resections, and IORT delivery site.

On the basis of this experience, we plan to start a phase II study to evaluate the efficacy of IORT as an early boost according to tumor site, distin-

guishing between primary or recurrent tumors, and IORT delivery site.

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