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CLINICAL INVESTIGATION

INTRAOPERATIVE RADIOTHERAPY FOR PAROTID CANCER: A SINGLE-INSTITUTION EXPERIENCE

Youssef H. Zeidan, M.D., Ph.D.,* Kevin Shiue, B.S.,* Daniel Weed, M.D.,* Peter A. Johnstone, M.D.,† Colin Terry, M.S.,‡ Stephen Freeman, M.D.,§ Edward Krowiak, M.D.,§ Robert Borrowdale, M.D.,§ Tod Huntley, M.D.,§ and Alex Yeh, M.D.*

*Department of Radiation Oncology, Methodist Hospital, Indianapolis, IN; †Department of Radiation Oncology, Indiana University, Indianapolis, IN; ‡Methodist Research Institute, Methodist Hospital, Indianapolis, IN; §CENTA Otolaryngology, Indianapolis, IN

Purpose: Our practice policy has been to provide intraoperative radiotherapy (IORT) at resection to patients with head-and-neck malignancies considered to be at high risk of recurrence. The purpose of the present study was to review our experience with the use of IORT for primary or recurrent cancer of the parotid gland.
Methods and Materials: Between 1982 and 2007, 96 patients were treated with gross total resection and IORT for primary or recurrent cancer of the parotid gland. The median age was 62.9 years (range, 14.3–88.1). Of the 96 patients, 33 had previously undergone external beam radiotherapy as a component of definitive therapy. Also, 34 patients had positive margins after surgery, and 40 had perineural invasion. IORT was administered as a single fraction of 15 or 20 Gy with 4–6-MeV electrons. The median follow-up period was 5.6 years.
Results: Only 1 patient experienced local recurrence, 19 developed regional recurrence, and 12 distant recurrence. The recurrence-free survival rate at 1, 3, and 5 years was 82.0%, 68.5%, and 65.2%, respectively. The 1-, 3-, and 5-year overall survival rate after surgery and IORT was 88.4%, 66.1%, and 56.2%, respectively. No perioperative fatalities occurred. Complications developed in 26 patients and included vascular complications in 7, trismus in 6, fistulas in 4, radiation osteonecrosis in 4, flap necrosis in 2, wound dehiscence in 2, and neuropathy in 1. Of these 26 patients, 12 had recurrent disease, and 8 had undergone external beam radiotherapy before IORT.
Conclusions: IORT results in effective local disease control at acceptable levels of toxicity and should be considered for patients with primary or recurrent cancer of the parotid gland. © 2011 Elsevier Inc.

Intraoperative radiotherapy, Head and neck, Cancer, Parotid, IORT.

INTRODUCTION

Tumors of the salivary glands are relatively rare, representing 3–6% of all head-and-neck neoplasms and 0.3% of all malignancies (1). Parotid gland tumors account for 50–85% of salivary gland tumors, with 50–80% of parotid tumors benign and 20–30% malignant. Definitive treatment of these tumors primarily involves surgical resection and adjuvant radiotherapy (RT) for lesions at high risk of recurrence. The 5-year risk of local recurrence after surgical resection alone is 25–30%. The addition of adjuvant RT further decreases this risk to 9–10% (2–4). Disease recurrence carries a poor prognoses owing to invasion of vital structures within the head and neck.

Radiotherapy is commonly used as adjuvant treatment or, rarely, as definitive treatment when surgical resection is not possible. Delivering RT at resection of parotid cancers is particularly helpful in cases in which gross or microscopic residual disease is present or for recurrent disease (5). The safety and effectiveness of intraoperative RT (IORT) for head-and-neck cancer (HNC) have been established in several studies from our institution and others (6–8). Two forms of IORT have been studied for HNC: high-dose-rate brachytherapy (9) and external electron beam RT (6, 7).

Historically, IORT was first introduced in the United States in the 1970s after advances in anesthesia settings. One of the first applications of IORT was for abdominal and gynecologic malignancies (10). IORT is applied directly to the tumor bed, with customized shielding of adjacent healthy tissues and critical structures (11–13). When combined with external beam RT (EBRT), IORT has the advantages of reducing the

Reprint requests to: Youssef H. Zeidan, M.D., Ph.D., Department of Radiation Oncology, Methodist Hospital, 1704 N. Capitol Ave., B335, Indianapolis, IN 46206-1367. Tel: (317) 962-8881; Fax: (317) 962-6904; E-mail: youssefzaidan@gmail.com

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volume of the radiation boost field, limiting the dose to radiosensitive structures, and increasing the effective dose. The disadvantages include the need for extra manpower and utilities and the addition of approximately 45 minutes to the total operative time.

Intraoperative RT for HNC was implemented at Methodist Hospital, Indianapolis, beginning in 1982 in hopes of improving patient outcomes and local disease control. Previously, our group reported on the outcomes of this approach in cervical metastases (14) and skull base tumors (15) . However, little is known about the effectiveness of IORT in parotid cancer. The purpose of the present retrospective study was to review a single-practice experience over 26 years with the use of IORT in patients with primary or recurrent cancer of the parotid gland.

METHODS AND MATERIALS

Study population

The present retrospective study was approved by the institutional review boards at Methodist Hospital and St. Vincent Hospital (Indianapolis, IN). All patients were treated by members of a single practice. Between August 1982 and July 2007, 96 patients were treated at Methodist Hospital for primary or recurrent cancer of the parotid gland (Table 1). The median age of the study population at primary or salvage surgery with IORT was 62.9 years (range, 14.3–88.1). The general indications for treatment included *(1)* tumor that could not be dissected with obviously clean margins from vital nerves, muscles, the carotid artery, or bony structures; *(2)* disease that was thought to be more aggressive than usual; *(3)* suspected close or positive margins or cases of suspected residual microscopic disease; and *(4)* previous EBRT. A total of 33 patients had undergone previous RT, with a median dose of 60 Gy (range, 17.50–70.0), and a median interval from completion of previous RT to IORT of 8.7 months (range, 0.8–71.6). All patients provided informed consent at consultation in the radiation oncology department before surgery.

Treatment

In the present study, 46 patients were treated with salvage surgery and 50 with primary surgery. Surgical removal of all resectable disease was attempted before the application of IORT to the tumor bed. All patients received IORT at surgery. Between 1982 and 2003, the patients were transported between the operation suite and the linear accelerator under general anesthesia for IORT. Starting in 2003, a mobile electron unit (Mobetron, Intraop, Santa Clara, CA) was used in the operating suite. The area at greatest risk of recurrence was delineated, with input from the surgeon. The appropriate cone was chosen by the radiation oncologist, and manually positioned over the target area. Critical structures inside the cone were covered with pliable 1–2-mm-thick lead shields. A thin layer of petrolatum-soaked gauze was used as bolus if desired by the radiation oncologist. Blood or other accumulated fluids in the operative bed were suctioned before treatment. When using the Mobetron, the cone was fixed to the operating table using a special clamp, and the applicator was docked to the linear accelerator using the guidance of a laser docking system.

Table 1. Patient characteristics

Characteristic	Patients (%)
Gender	
Male	60 (62)
Female	36 (38)
Treatment	
Primary	50 (52)
Salvage	46 (48)

Data in parentheses are percentages.

The dose, cone size, electron energy, and the use of a bolus were set at the discretion of the treating physician. The treatment cones ranged from 3.0 to 10.2 cm in diameter. The electron energies were 4 MeV in 30 patients, 5 MeV in 57 patients, and 6 MeV in 9 patients, all dosed to the maximal dose. Of the 96 patients, 57 received 15 Gy and 39 received 20 Gy. Postoperative EBRT was prescribed to 55 patients at the discretion of the attending radiation oncologist. The median dose was 45 Gy (range, 20–66). Overall, 18 patients received some type of chemotherapy (*e.g.*, adjuvant, palliative, neoadjuvant). Follow-up consisted of clinical examinations with radiographic follow-up as clinically indicated.

Statistical analysis

The endpoints analyzed were local control, recurrence-free survival (RFS), and overall survival (OS). All events were measured from the date of primary or salvage surgery with IORT. Local failure was defined as tumor recurrence anywhere within the IORT field. Failures outside the IORT field but within or adjacent to the parotid bed were considered regional. The 1-, 3-, and 5-year estimates of RFS and OS were derived using the Kaplan-Meier method, with comparisons among groups performed using 2-sided log–rank tests. A Cox proportional hazards model was used to identify characteristics predictive of survival and disease recurrence. Univariate and multivariate analysis were used. All tests were two-tailed comparisons, and the acceptable probability of a type I error was set as $< .05$ for statistical significance.

Not all patients had complete charts with respect to the variables analyzed. As such, the statistical analyses performed considered only those patients with the relevant information, with patients having no record of, or no data on, a specific variable excluded from that particular analysis. All patients had complete records with respect to the endpoints studied.

RESULTS

Disease characteristics

In the present study, the patient population consisted of 96 patients who underwent IORT for primary or recurrent parotid tumors. The most common histologic subtypes were mucoepidermoid carcinoma in 20, followed by squamous cell carcinoma in 15 patients. The other subtypes encountered included adenoid cystic carcinoma in 11, adenocarcinoma in 10, and others. The pathologic specimens revealed that 40 patients had perineural invasion, 33 had positive margins, 5 had lymphovascular (LVI) or angiolymphatic (ALI) invasion, 3 had extracapsular extension, 3 had vascular invasion, 18 had dermal invasion, and 3 had carotid involvement. Also, 40 patients had clinical cranial nerve VII paresis. The median tumor size was 2.5 cm (range, 0.7–9.5). The disease characteristics are summarized in Table 2.

Local control, recurrence, and recurrence-free survival

A total of 32 patients (33%) experienced recurrent disease (local, regional, or distant) within a median follow-up of 5.6

Table 2. Disease characteristics at surgery with IORT

Characteristic	Patients (%)
Histologic type	
Mucoepidermoid	20 (21)
Squamous	15 (16)
Adenoid cystic	11 (11)
Adenocarcinoma	10 (10)
Other	40 (42)
Tumor size (cm)	
≤2	45 (47)
2.1–4	38 (39)
>4	13 (14)
Perineural invasion	40 (42)
Positive margins	33 (34)
Seventh nerve paralysis	40 (42)
LVI/ALI	5 (5)
ECE	3 (3)
Vascular invasion	3 (3)
Dermal invasion	18 (19)
Carotid involvement	3 (3)

Abbreviations: LVI = lymphovascular invasion; ALI = angiolymphatic invasion; ECE = extracapsular extension.

Data in parentheses are percentages.

years. Using the Kaplan-Meier method, the estimated median interval to any type of recurrence was 9.4 years.

Only 1 patient (1%) experienced local recurrence in the IORT field; 19 patients (20%) experienced regional recurrence, and 12 (13%) experienced distant recurrence. Among the primary surgery patients, 3 regional and 7 distant recurrences developed compared with 16 regional and 5 distant recurrences among patients treated for recurrent disease. A comparison between patients with local or regional recurrence and those with distant recurrence yielded no significant predictors for the type of recurrence experienced.

The RFS rate after IORT was 82.0%, 68.5%, and 65.2% at 1, 3, and 5 years, respectively. The corresponding RFS rates were 92.4%, 84.3%, and 77.8% for the primary surgery patients and 69.2%, 48.1%, and 48.1% for the patients with recurrent disease (Fig. 1).

The following characteristics were predictive of recurrence-free survival on univariate analysis: positive vs. negative margins (p = .042),), lymph node status (p < .001), presence vs. absence of LVI or ALI (p = .006), presence vs. absence of dermal invasion (p = .006), and previous chemotherapy (p < .001; Table 3).

Additional analysis was performed to investigate the potential factors prognostic of recurrence after IORT. We used a hazard ratio (HR) model to study the continuous factors, including age, tumor size, and cone size. Larger tumor size was predictive of recurrence in general (HR, 1.29; p = .022, per 1 cm increase in size; Table 4). Multivariate analysis showed surgery type (primary vs. recurrent; p = .04) and tumor size (p = .002) to be predictive of recurrence.

Overall survival

Of the 96 patients, 39 were alive at the last follow-up visit. The OS rate at 1, 3, and 5 years after IORT was 88.4%, 66.1%, and 56.2%, respectively (Fig. 2). Patients with primary surgery had corresponding OS rates of 88.1%, 76.1%, and 65.7% compared with 87.2%, 59.0%, and 48.3% for patients with recurrent disease. Patients undergoing IORT as primary treatment survived for a median of 10.8 years after IORT compared with 4.0 years for patients undergoing salvage treatment (p = .19; Fig. 3).

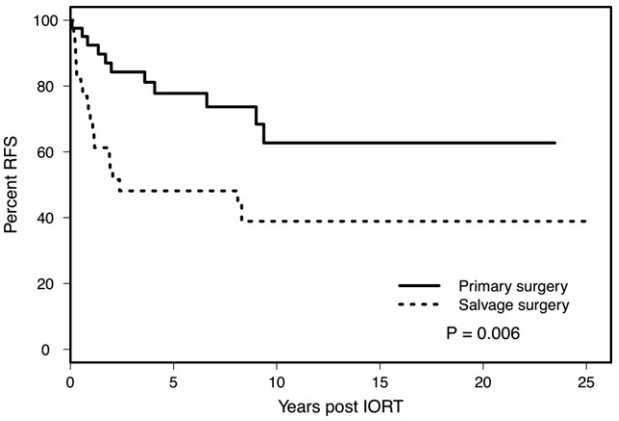

Fig. 1. Kaplan-Meier recurrence-free survival (RFS) by surgery type. IORT = intraoperative radiotherapy.

Of the patients and disease characteristics analyzed, the presence of LVI or ALI, lymph node status, presence of dermal invasion, and previous treatment regimens were predictive for OS on univariate analysis (Table 3). The patients whose surgical pathologic findings indicated the presence of LVI or ALI survived for a median of only 0.6 years after IORT compared with 9.8 years for patients without LVI or ALI (p < .001). The patients whose surgical pathologic findings indicated the presence of dermal invasion survived for a median of only 3.8 years after IORT compared with 10.9 years for patients without dermal invasion (p = .02).

Our analysis revealed that the survival of patients undergoing salvage surgery was influenced by previous treatment. The patients treated with previous chemotherapy survived for a median of only 3.6 years after IORT compared with 10.9 years for patients without previous chemotherapy (p = .018; Table 3).

In addition, we used a HR model to evaluate the continuous (rather than categorical) patient and treatment characteristics. The older patients, larger IORT cone size, and tumor size were predictive of decreased survival (HR, 1.04; p < .001; HR, 1.34, p = .001; HR, 1.30; p = .005, respectively; Table 4). On multivariate analysis, only patient age was predictive of survival (p = .011).

Complications

No perioperative fatalities or infections were noted. Complications occurred in 26 patients (27%; Table 5). Of the 26 patients, 7 had postoperative vascular complications, 6 developed trismus, 4 developed radiation osteonecrosis, 4 developed fistulas, 2 developed flap necrosis, 2 developed

Table 3. Statistical correlation of disease characteristics with survival outcomes (univariate analysis)

Characteristic (%)	Median RFS (y)	*p*	Median OS (y)	*p*
Primary vs. recurrent		.006		.19
Parotid primary therapy (52)	NE		10.8	
Parotid salvage therapy (48)	2.4		4	
Perineural invasion		.174		.065
Yes (42)	8.1		4	
No (58)	NE		12.7	
Margins		.042		.263
Positive (34)	8.1		6.1	
Negative (66)	NE		10.8	
Intraoperative dose (Gy)		.553		.877
15 (59)	9.0		5.0	
20 (41)	NE		4.0	
Seventh nerve paralysis		.14		.185
Yes (42)	8.1		6.1	
No (58)	NE		12.7	
LVI/ALI		.006		< .001
Yes (5)	2		0.6	
No (95)	NE		9.8	
ECE		NA		NA
Yes (3)	9		NE	
No (97)	NE		7.2	
Positive lymph nodes		< .001		< .001
Yes (21.9)	0.9		1.2	
No (81)	NE		10.9	
Vascular invasion		NA		NA
Yes (3)	4.1		2.4	
No (97)	NE		8.2	
Dermal invasion		.006		.02
Yes (19)	4.1		3.8	
No (81)	NE		10.9	
Carotid involvement		NA		NA
Yes (3)	2.4		7.2	
No (97)	NE		9.8	
Previous treatment		.611		.144
RT alone (45)	1.7		1.9	
Surgery alone (45)	8.1		7.1	
Surgery plus RT (10)	2		7.3	
Previous chemotherapy		< .001		.018
Yes (16)	1.2		3.6	
No (84)	NE		10.9	
Adjuvant EBRT		.919		.217
Yes (57)	9.4		9.8	
No (43)	NE		7.1	

Abbreviations: RFS = recurrence-free survival; OS = overall survival; NE = not estimable; NA = not applicable; RT = radiotherapy; EBRT = external beam radiotherapy; other abbreviations as in Table 2.

wound dehiscence, and 1 developed neuropathy. Also, 12 of these 26 patients had recurrent disease, and 8 had undergone EBRT before IORT.

None of the studied prognostic factors in Tables 3 and 4 correlated significantly with the reported complications. Of the patients with vascular events, 3 had strokes, 2 transient ischemic attacks, and 2 hematomas. Six of these patients had received previous chemotherapy and demonstrated unfavorable pathologic features, such as LVI, dermal invasion, or facial nerve paralysis.

Table 4. Correlation of longitudinal factors with outcomes

	HR (95% CI), *p*	
Factor	Recurrence	Survival
Age	1.02 (0.99–1.04), .167	1.04 (1.02–1.06), < .001
Tumor size	1.29 (1.06–1.57), .022	1.30 (1.10–1.54), .005
Cone size	1.16 (0.94–1.43), .165	1.34 (1.13–1.59), .001

Abbreviations: HR = hazard ratio; CI = confidence interval.

DISCUSSION

Tumors involving the parotid gland are routinely managed by surgery. Adjuvant therapy is a function of the histology of the lesion and can involve EBRT or, less frequently, chemotherapy. Despite multiple advances in surgical techniques and RT, parotid carcinomas continue to take a high toll in patient mortality and morbidity. Our experience with this patient population during the past 25 years indicates that adding IORT improves disease control with acceptable treatment-related complications.

Few comparable reports are available in the literature. In a recent study, Chen *et al.* (5) evaluated the University of California, San Francisco, experience with IORT for recurrent salivary gland tumors. Of these lesions, 34% were parotid cancers. The study reported a 5-year local control rate of 82% for those patients who received IORT vs. 60% for those who received surgery alone (5).

Other radiation modalities have yielded promising results for advanced parotid disease. Garden *et al.* (4) reported a 9% local recurrence rate in patients with malignant tumors of the parotid gland treated with postoperative EBRT (4). Buchholz *et al.* (16) reported a local recurrence rate of 7.7% in patients with locally advanced salivary gland malignant cancers treated with fast neutron RT. Without randomized clinical trials comparing these different modalities, treatment selection remains to be ruled by clinical judgment. Factors influencing such selection include patient characteristics, previous treatment, available equipment, and clinician's expertise.

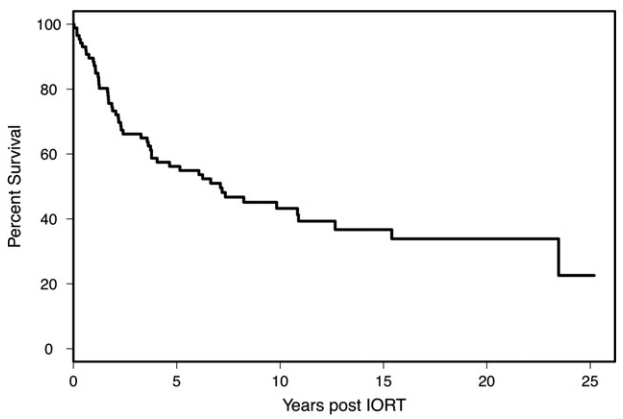

Fig. 2. Kaplan-Meier overall survival (OS) for all patients. IORT = intraoperative radiotherapy.

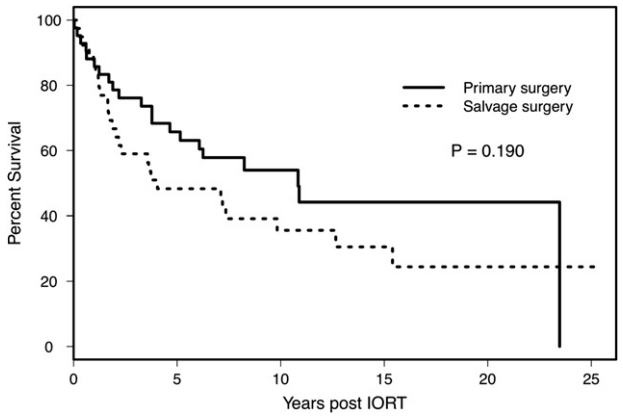

Fig. 3. Kaplan-Meier overall survival (OS) by surgery type. IORT = intraoperative radiotherapy.

The utility of IORT has been well documented in published studies, particularly for patients with recurrent HNC (17). The University of California, San Francisco, experience using electron beam IORT with 137 patients was reported by Chen *et al.* (7). The OS and in-field control rates were 36% and 61%, respectively, at 3 years. In another report by Nag *et al.* (18), 38 patients underwent IORT. The local control rate for this patient cohort was 13% after 2 years (18). Pinheiro *et al.* (19) analyzed the Mayo Clinic experience with 44 patients who underwent IORT for recurrent HNC. The 5-year in-field control rate was 41% for those with squamous cell carcinoma and 52% for those with other types (19).

Fewer studies have considered the utility of IORT for primary HNC. Nag *et al.* (20) studied 65 patients (53 with primary HNC) who received high-dose-rate IORT. The 5-year local control and OS rates were 69% and 42%, respectively (20). Recent studies have emphasized the effect of the time lag between surgery and RT for HNC patient outcomes. Importantly, Ang *et al.* (21) reported improved survival and locoregional control when patients with advanced HNC received RT within 11 weeks of surgery. In this setting, IORT has the advantage of bridging the time gap between surgery and starting RT.

This discrepancy of the reported results can be attributed to the heterogeneity in the patient population, disease sites, and treatment (both surgical and RT) approaches used at different centers. In an attempt to limit such heterogeneity, we analyzed a subpopulation of HNC patients with parotid disease treated by members of the same practice. To our knowledge, the present report is the largest experience of using IORT for cancer involving the parotid gland. Our results hold major implications for practicing radiation oncologists and head-and-neck surgeons. Such results are important when counseling patients on the appropriateness of IORT for their parotid disease, the prognosis, and the potential complications of such therapy.

Table 5. Complications of surgery and IORT for parotid tumors

Complications	*n* (%)
Vascular complications	7 (7.3)
Trismus	6 (6.3)
Radiation osteonecrosis	4 (4.2)
Fistulas	4 (4.2)
Flap necrosis	2 (2.1)
Wound dehiscence	2 (2.1)
Neuropathy	1 (1.0)
Total	26 (27)

Several patient and disease characteristics were also identified as predictors of OS and recurrence-free survival. In agreement with previous reports, tumor size was predictive of local recurrence in our cohort. Patients with gross residual disease have poor local control across most reports. Considering the risk/benefit ratio, some investigators have discouraged using IORT in the setting of gross residual disease, except for palliation (22).

The present study also had its limitations and weaknesses. Our cohort was insufficiently large to dissect the real benefit attributable to IORT. Such analysis is complicated because most patients received different types of adjuvant chemotherapy and RT before and/or after IORT. This question will be best addressed in a randomized Phase III clinical trial. Second, only patients who had information available regarding the variable/factor studied were included. Omitting patients with unavailable records could have introduced a potential bias in the results.

Several questions remain unanswered. Although most studies used IORT doses of 12–20 Gy, the published data still lack clinical evidence for the optimal IORT dose. In our experience, the IORT dose did not significantly influence OS or RFS, although most patients (59%) received 15 Gy (Table 3). Another unresolved question relates to combining IORT with adjuvant EBRT. In one study, it was reported that patients who received additional EBRT had a 79% local control rate compared with 50% for those who did not (23). As listed in Table 3, our analysis has confirmed the improved OS for patients who received adjuvant EBRT, in agreement with a previous study (20). In contrast, others have reported no difference in survival or local control when patients received additional EBRT (19). Third, it would be interesting to determine how the molecular signature of parotid tumors would influence the clinical response to IORT. For instance, tumor human papillomavirus status is gaining increasing significance when planning RT for HNC patients. Future studies at the clinical and molecular levels are expected to shed light on these questions and others.

Our overall complication rate of only 26% was quite encouraging, given the number of patients with unfavorable features included in the study (Table 2). Past experience with IORT in HNC patients has major complications ranging from 6.5% to 28.4% (6, 7, 24–26). The etiology of our reported complications is likely multifactorial, including tumor invasion of critical structures and previous treatments, in addition to the treatment delivered. Although the ideal IORT dose is yet to be determined, previous experience indicates greater incidence of complications with IORT

doses >20 Gy in HNC patients (24). In addition to the dose, other factors that need to be considered to minimize complications, including cone size, proper shielding, and patient comorbidities.

CONCLUSIONS

This report is the largest published discussing IORT for parotid lesions. The 5-year OS rate of 56.2% and RFS rate of 65.2% compare favorably to historical controls. The major contribution of IORT for managing parotid tumors is improving local control with only 1% local recurrence observed. However, the incidence of regional and distant failure continue to be unacceptably high, underscoring the importance of additional EBRT and the need for developing novel systemic therapy. The present study also identified disease characteristics that influence the clinical response to IORT. Such prognostic factors are important to remember when considering adding IORT for a patient with parotid tumor. Taken together, our retrospective study supports the initiation of a multi-institutional prospective Phase III trial of IORT for parotid cancer.

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