Intraoperative radiation therapy for locally advanced and recurrent head and neck cancer

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Abstract. The purpose of the present study was to present a single institution experience with intraoperative radiation therapy (IORT) for patients with head and neck cancer (HNC). The present study included all patients with HNC treated consecutively with IORT at Loyola University Medical Center between January 2014 and December 2018. Charts were reviewed for patient and tumor characteristics, IORT technical details, IORT-induced adverse events and treatment outcomes. The study included 23 eligible patients. Median patient age was 66 years (range, 34-91 years). Tumor sites included the parotid gland (43%), lymph nodes (43%), oral tongue (9%) and ear (4%). A total of 48% of patients received IORT upfront with or without postoperative adjuvant external beam radiation therapy (EBRT), whereas 52% received salvage IORT after local tumor recurrence. The median prescribed IORT dose was 7.5 Gy (range, 5-14 Gy) in a single fraction prescribed to 5 mm depth with flat applicators (median diameter, 5 cm). A total of 92% of patients did not experience wound healing complications. One patient (4%) developed postoperative acute thromboembolic stroke and a second patient (4%) experienced protracted wound healing. At a median follow up of 36 months (range, 2-81 months), overall survival was 52%. In addition, 48% of patients were reported to have no evidence of disease, and although two had died of unrelated causes, 13% of patients were alive with disease and 39% died with the disease. The local-regional recurrence rate was 39% (median time to local recurrence, 11 months; range, 1-34 months), the rate of distant metastasis was 35% (median time to distant metastasis, 16 months; range, 4-40 months), and 21% of patients had both local-regional recurrence and distant metastases. The percentages of local-regional recurrence and distant metastases among patients receiving salvage IORT were 58 and 50% respectively, compared with 18 and 18% respectively in those receiving upfront IORT with or without adjuvant EBRT. In the present single institution retrospective study, it was concluded that IORT for patients with locally advanced and recurrent HNC was a safe treatment modality, with tumor control comparable to historical IORT data. Larger prospective studies are needed to further assess the utility of IORT in the management of locally advanced and recurrent HNC.

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Introduction

A large proportion of head and neck cancer (HNC) patients present with local or regionally advanced disease, as signs and symptoms of early disease are often minimal and nonspecific (1). Despite technological advances in radiation therapy (RT) techniques, about 40% of local-regionally advanced HNC will persist or recur after first line treatment, namely surgery and adjuvant or definitive external beam radiation therapy (EBRT) with or without chemotherapy (2). Local-regional recurrent HNC are usually managed with surgery and or reirradiation (3). Reirradiation with EBRT of local-regionally recurrent HNC comes with risk of treatment-related toxicity, including death (4). Alternatively, intraoperative radiation therapy (IORT) has been shown to improve outcomes from salvage surgery in patients who previously received EBRT; in the primary setting, IORT can be used as a boost to optimize local control (5).

IORT generally delivers a single dose of radiation at the time of resection of HNC (5). There are multiple modalities used for IORT, including orthovoltage photons, electrons (EIORT), and brachytherapy. This study includes HNC patients who received IORT delivered via INTRABEAM (Carl Zeiss, Oberkochen, Germany).

The IORT doses are typically higher than the doses delivered during individual fractions from EBRT, which reduces tumor cell survival but may also worsen treatment-related toxicity of normal tissue (5). However, the low energy x-ray

beam generated with the INTRABEAM source provides a quick dose drop off which naturally limits the irradiation of critical structures in an IORT setting. By restricting the treatment volume to the surgical bed, the dose to surrounding normal tissue is minimized, and thus the risk of treatment-related toxicity is reduced. The purpose of this study is to present a single institution experience with IORT for HNC patients.

Materials and methods

Patients. The present retrospective study was approved by the institutional review board (IRB #214428) at Loyola University Chicago. The present study that included all HNC patients treated consecutively with IORT at Loyola University Medical Center between January 2014 and December 2018. Patients with benign tumors confirmed by pathology report were excluded. All patients were treated per institutional protocols at the discretion of the treating physician and were not part of any clinical trials.

Treatment. All patients received IORT in the operating room with the INTRABEAM PRS 500 in a single fraction following the resection of the tumor volume (6). The INTRABEAM system consists of a low energy x-ray source (XRS), a source positioning stand, and a mobile cart holding the XRS control unit and user interface to set the treatment dose and monitor the treatment delivery (Fig. 1). The XRS contains a miniaturized accelerator designed to accelerate electrons at 50 keV down a thin 10 cm long aluminum drift tube. The electrons impinge on a thin gold target to emit bremsstrahlung x-rays isotropically with a mean energy of approximately 20 keV to provide a uniform dose distribution. The INTRABEAM floor stand provides 6 degrees of freedom to hold and precisely position the XRS onto the treatment area. The control unit is used to perform quality assurance, set the prescription dose and monitor the system performance during irradiation time.

Patients were initially seen before surgery by the radiation oncologist to discuss all potential treatment options and were then consented for IORT. Following the tumor resection by the otolaryngology team, the radiation oncology team was called to deliver IORT to the tumor bed. The INTRABEAM stand, XRS and treatment console were brought into the operating room. First, the XRS unit producing 50kV x-rays underwent quality assurance to ensure appropriate straightness of XRS drift tube, and to measure the daily output of the XRS. All IORT treatments were delivered with Flat applicators (7). These applicators are designed for superficial treatments with INTRABEAM and contain a flattening filter that converts the spherical dose distribution from the XRS into a homogenous planar dose distribution at 5-9 mm depths, depending on the applicator size. The median applicator size for all IORT treatments was 5 cm (range 3-6 cm) and was selected by the treating radiation oncologist to fully cover the treatment target, a high-risk area within the tumor bed that was highlighted with clips. Wet gauze was employed to protect organs at risk (blood vessels and nerves) when applicable. The INTRABEAM machine was draped and placed under sterile conditions. The flat applicator was attached to the XRS unit on the INTRABEAM floor stand. Finally, the applicator was placed against the highlighted area at risk.

Dose conversion. It is common and accepted practice to assume a relative biological effectiveness (RBE) value of 1 for high-energy electrons in the range used in standard linear accelerators and the Mobetron IORT system, with cell survival assays comparing high energy electrons to reference photon beams of 6 MV and Co-60 showing no expectation for elevated RBE. In the case of the 50 kVp X-rays produced by the INTRABEAM system, the low energy photons would be expected to have an elevated RBE. While clinical data are not available for elevated RBE of low energy photons in the intraoperative setting, pre-clinical experiments using the INTRABEAM system, low energy electrons, and radiobiology-based computer simulations have been performed demonstrating an increased expectation for elevated RBE. For 50 kV x-rays from INTRABEAM in water-equivalent phantom at 8.1 mm from the applicator surface, the RBE in reference to 6-MV photons ranges from 1.26 to 1.42 for 4 different cell lines (8). Experiments and simulations evaluating the impact of low energy electrons and photons show a clear increase in the damage potential as the photon and electron energy is reduced (9-11). While consensus data are premature, owing to the large difference in beam quality between clinical IORT systems, a direct biological equivalence of similar dose between platforms is unlikely. As such, it is practical to assume a high likelihood for the INTRABEAM system to have a higher RBE value than other IORT platforms. For this report, all prescribed IORT doses were converted according to the 'TARGIT to V4.0' calibration factors provided by Zeiss to provide a more accurate estimation of the delivered dose to the treatment targets as suggested by recent publications (12).

Analysis. Endpoints analyzed were overall survival, local-regional recurrence, and distant metastasis. Recurrence was defined as radiographic, clinical, or pathologic evidence of recurrence. If recurrence was found at the IORT site, it was considered local recurrence; if recurrence involved lymph nodes of the neck, it was considered regional recurrence. Rates of overall survival, local-regional recurrence and incidence of distant metastases were calculated with the Kaplan-Meier method using IBM SPSS Statistics 27 (IBM, Armonk, NY). The comparison between upfront and salvage IORT groups and original site of disease was performed with a two-sided log-rank test, where statistical significance was defined for $P<0.05$.

Results

Patients. Between January 2014 and December 2018, 24 HNC patients were treated consecutively with IORT at our institution. This study included 23 of these HNC patients, as 1 patient was excluded for a pathology report significant for a benign Warthin tumor. Patients' median age at time of IORT was 66 years (range: 34-91 years). Per the surgical pathology report, the most common histology was squamous cell carcinoma (SCC) (70%, 16 patients). Two patients (9%) had salivary duct carcinoma, and one patient (4%) had adenocarcinoma, favoring salivary duct carcinoma. One patient (4%) had poorly differentiated carcinoma, possibly SCC. One patient (4%) had acinic cell carcinoma. One patient (4%) had pleomorphic adenoma (carcinoma *in situ*). One patient (4%)

Figure 1. INTRABEAM device and stand. The insert shows an example flat applicator.

had mammary analogue secretory carcinoma. Median size of the tumor on surgical pathology was 2.7 cm (range 0.3-4.5 cm) (Table I). 17% of patients were female, 83% were male. 13% were active smokers, while 87% were former smokers. 9% had a greater-than-40 pack-year smoking history, 30% had a 20-40 pack-year smoking history, 30% had an under-20 pack-year smoking history, and 30% did not disclose a pack-year smoking history. 96% of patients identified as white, and 4% (1 patient) identified as Asian (Table II). 48% of patients (11 patients) received IORT upfront with or without postoperative adjuvant external beam radiation therapy (EBRT), while 52% (12 patients) received salvage IORT after local tumor recurrence. Patient tumor sites included parotid gland (10 individuals, 43%), lymph nodes (10, 43%), oral tongue (2, 9%), and ear (1, 4%) (Table I). Of the 23 patients, 6 patients had primary parotid disease, 1 patient had acinic cell carcinoma, 1 patient had primary left temporal skin cancer, 5 patients had skin HNC with local-regional metastasis, 4 patients had primary oropharyngeal/tongue disease, 3 patients had cancer to the supraglottis, 1 patient had left supraclavicular and posterior pharyngeal disease, 1 patient had right tragus disease, and 1 patient had left neck squamous cell carcinoma with unknown primary. No patients had distant metastatic disease at the time of presentation.

Of the 23 patients, 8 patients (35%) had treatment of unilateral parotid gland, 2 patients had treatment of unilateral parotid bed, 5 were treated at unilateral neck, 1 at bilateral neck, 2 at a singular right neck node, 1 at left supraclavicular region, 1 patient received treatment to the head and neck, 2 at the oral tongue, and 1 at right ear.

The median prescribed dose was 7.5 Gy (range: 5-14 Gy) prescribed to a depth of 5 mm. The corresponding median beam-on time was 30.25 min (range: 12.02-54.80 min). The median resulting dose at the surface of the treatment site was 13.68 Gy (range: 5.95-29.88 Gy). After the radiation was delivered, the flat applicator was removed promptly.

Using 'TARGIT to V4.0' calibration factors resulted in converted dose values averaging 15% higher (σ=0.7%), with a median recalculated dose of 8.57 Gy (range 5.73-16.18 Gy). The converted surface doses were 17% higher, with a median recalculated dose of 15.87 Gy (range: 6.93-35.26 Gy).

After surgery, patients were hospitalized for postoperative observation. Median duration of hospital stay was 2 days (range 1-9 days). Median follow up was 36 months (range 2-81 months), with follow up reported as the last office visit with any physician.

Treatment outcomes. Twelve patients (52%) were alive at last follow up, though four of these patients were considered lost to follow up with last appointment dated more than two years prior to time of analysis. Three patients (13%) had a status of alive with disease (AWD) at last follow up (two of these patients were lost to follow up), whereas nine patients (39%) were alive with no evidence of HNC (NED) at last follow up (two of these patients were lost to follow up). Two patients (9%) died with a status of NED (one patient was diagnosed with primary bile duct carcinoma and declined further treatment, and the other patient died from acute respiratory failure due to COVID pneumonia). Nine patients (39%) died with either persistent or recurrent disease (DWD). Overall survival is presented in Fig. 2A.

For individuals receiving upfront vs. salvage IORT, the cumulative proportion surviving at 1, 2, 3 and 4 years is 91, 81, 81, 81% respectively for upfront IORT and 67, 67, 38 and 16% respectively for salvage IORT. Patients who received upfront IORT had significantly improved overall survival compared to those who received IORT as salvage therapy (Fig. 2B) (P=0.01). Of the eleven patients who received upfront IORT, eight patients were NED and two patients were AWD at the time of last follow up, though two of these patients were lost to follow up. Of the twelve patients who received salvage IORT, one patient was AWD and two patients were NED at the time of last follow up; however, both of these patients were subsequently lost to follow up.

For individuals receiving IORT at the primary site (i.e., parotid, parotid bed, oral tongue) vs. the neck, the cumulative proportion surviving at 1, 2, 3, and 4 years is 92, 92, 92, and 74% respectively for primary site IORT and 60, 49, 12 and 12% respectively for IORT involving the neck. Patients who received IORT to primary site also had significantly improved overall survival compared to those who received IORT to the neck, as shown in (Fig. 2C) (P<0.001). The distribution of origination sites was as follow: ten received IORT to the neck (44%), eight to the parotid (35%), two to the parotid bed (9%), two to the oral tongue (9%) and one to the ear (4%).

Fig. 3A presents the incidence of local recurrence and of distant metastases. The local-regional recurrence rate was 39% (median time to local recurrence was 11 months, range 1-34 months), compared to a lower 35% rate of distant metastasis (median time to distant metastasis was 16 months, range 4-40 months). 21% of the patient cohort had both local-regional recurrence and distant metastases. Of the 8 patients with distant metastasis, 3 had bony metastasis, 5 had lung metastasis. The percent of local-regional recurrence and distant metastases among patients receiving salvage IORT was 58 and 50% respectively, compared to 18, and 18% respectively in those receiving upfront IORT with or without adjuvant EBRT. The incidence rates of loco-regional recurrence and

Table I. Tumor characteristics, treatment and outcomes.

Patient no.	Tumor site	Histology	Tumor size, cm	Age at IORT, years	IORT dose, Gy	Upfront vs. salvage	Follow up (months)	Time to local-regional recurrence, months	Time to distant metastasis, months
1	Right cervical neck	SCC	4	54	7.5	Salvage	22	11.00	11.00
2	Right parotid	High grade salivary duct carcinoma	2.3	66	8	Upfront	70		
3	Oral tongue	Adenocarcinoma, favor low grade, well-differentiated salivary duct carcinoma	1.4	81	10	Salvage	38		40.00
4	Right parotid	Well-differentiated SCC	2	48	7.5	Upfront	50		
5	Left parotid	SCC	4.2	91	8	Upfront	12		
6	Head and neck	SCC	2.6	74	5	Upfront	11		
7	Left parotid	Poorly-differentiated SCC	3.1	80	5	Upfront	81		
8	Right neck node	Poorly-differentiated SCC	2.8	70	14	Salvage	28	26.00	
9	Left parotid	Moderately-differentiated SCC	3.4	66	5	Salvage	36		
10	Left parotid	SCC	4.5	59	5	Upfront	72		
11	Right parotid	Poorly-differentiated carcinoma, possibly SCC	1.1	71	5	Upfront	76		
12	Right neck	SCC	0.3	43	10	Salvage	6	4.00	
13	Neck	SCC	1.5	34	12	Salvage	2	1.00	
14	Right neck node	SCC	5.6	64	12	Salvage	26		26.00
15	Left Neck	SCC	3.1	72	12	Salvage	51		
16	Right neck	Acinic cell carcinoma	2.6	53	5	Upfront	7		4.00
17	Left subclavian	Poorly-differentiated SCC	4.1	60	5	Salvage	6	6.00	6.00
18	Oral tongue	Moderately-differentiated SCC	3	66	10	Salvage	5	5.00	5.00
19	Left parotid	Salivary duct carcinoma, poorly- differentiated, high grade	2.6	66	5	Upfront	39	14.00	21.00
20	Left parotid bed	Pleomorphic adenoma, carcinoma *in situ*	1.8	66	5	Upfront	52		
21	Right parotid bed	Mammary analogue secretory carcinoma	4.1	66	5	Upfront	56	34.00	
22	Right ear	Well-differentiated SCC	1.2	80	14	Salvage	40		
23	Right neck	SCC	2.9	86	12	Salvage	25	23.00	23.00

SCC, squamous cell carcinoma.

distant metastases was higher for patients receiving salvage IORT compared to those receiving IORT upfront (P=0.021), as shown in Fig. 3B.

Adverse events. There were no perioperative fatalities. One patient (4%) developed postoperative acute thromboembolic stroke, and one patient (4%) experienced protracted wound healing. 92% of patients did not experience wound healing complications. No patients developed evidence of carotid blowout, osteonecrosis or bone fracture.

Discussion

In select HNC patients who are surgical candidates with local-regional recurrence of a resectable tumor, salvage surgery with or without reirradiation is a good option (13). Despite multiple available treatment modalities for recurrent squamous cell HNC, the prognosis remains generally poor (14). This is consistent with our data, which showed significantly higher overall survival in patients undergoing upfront IORT compared to those receiving salvage IORT. Furthermore, our

Table II. Patient demographics.

Demographic	Number (%)
Sex	
Male	19 (83)
Female	4 (17)
Smoking status	
Active smoker	3 (13)
Former smoker	20 (87)
Smoking history of active and former smokers	
>40-pack-years	2 (9)
20-40 pack-years	7 (30)
<20 pack-years	7 (30)
Unknown	7 (30)
Race	
White	22 (96)
Asian	1 (4)

data reflected that overall survival was improved in IORT to primary sites compared to IORT involving the neck nodes, which translates to poorer prognosis compared to patients with local disease. For patients deemed good candidates for salvage therapy, previously irradiated tissue poses a challenge in treatment planning. Surgery is preferred for tumors that are away from at-risk organs and are amenable to surgical resection. Adverse events from reirradiation are a major concern, however, reirradiation may be recommended in situations where benefit outweighs risk (e.g., positive margins, perineural invasion, lymphovascular invasion, or extranodal extension), or if patients have unresectable, locally-recurrent HNC (15).

Hilal *et al* included 15 retrospective studies in their review of IORT as a treatment for HNC, concluding that while IORT seems to be a promising treatment modality for HNC, most available literature remains from single institutions (5). IORT is considered in patients with HNC recurrences for its advantage of decreasing treatment volume to the site directly observed in the operating room and avoiding organs at risk. This advantage is particularly valuable for neck recurrences in which tumors close to critical structures or surrounded by fibrosis from previous irradiation can be difficult to resect.

Two of the 15 studies reviewed by Hilal *et al* investigated electron IORT (EIORT) in the treatment of recurrent HNC (5). One such study by Zeidan *et al* reviewed 46 patients with parotid disease receiving a single dose of 15 or 20 Gy, median dose 15-20 Gy, with median follow up of 5.6 years and 3-year OS of 48% (16). This 3-year OS is greater than that of our study 3-year OS of 38% for those receiving salvage IORT. However, Zeidan *et al* also reported toxicity in 27% of individuals, including 7% with vascular toxicity, 6% with osteoradionecrosis, 4% with fistulas, 4% with flap necrosis, 2% with wound dehiscence, and 1% with neuropathy (16). Our study reported only 9% of patients with toxicity and no cases of vascular toxicity or osteoradionecrosis. Differences in IORT modality (Mobetron EIORT vs. INTRABEAM 50 kV x-rays) and in IORT dose (median dose 7.5 Gy vs. 15-20 Gy) are possible factors contributing to differences in toxicity between the Zeidan *et al* study and our study. Small population size and variety of disease sites in our study also could have affected outcomes.

Chen *et al* shared a retrospective study of a single institution experience using IORT as salvage therapy for recurrent HN cancer in 137 patients, revealing 3-year overall survival rate of 36%, with acceptable rates of complications (17). They concluded that IORT was a promising treatment modality for salvage therapy of HNC. Our study has 12 patients who underwent salvage IORT with 3-year overall survival rate of 38%, a similar OS rate to that of Chen *et al* but with minimal complications. Chen *et al* report median IORT dose of 15 Gy (range 10-18 Gy) whereas our study reports a median dose of 12 Gy (range 5-14 Gy) for those receiving salvage IORT. While the accurate dosimetry of the INTRABEAM source is still an active field of investigation, converting the prescribed TARGIT dose to the recommended 'V4.0' dose provided a more accurate estimate of the dose received by our patients' cohort (12). Overall, the median recalculated dose for those receiving IORT was increased by 15% to 13.68 Gy (range 5.73-16.18 Gy), which is a similar dose to that of the Chen *et al* study. To our knowledge, this is the first study to convert INTRABEAM IORT doses using the recommended 'TARGIT to V4.0' calibration factors. Future prescription of IORT treatment for HNC and retrospective analysis of HNC patients treated with INTRABEAM should report treatment doses using the V4.0 dose calibration protocol to allow for a meaningful comparison of outcomes vs. treatment modalities for IORT, such as soft x-rays and electron. The Chen *et al* study population was prescribed EIORT with 6-18 MeV electron beams delivered with a modified linear accelerator or 4-12 MeV of electron therapy with a Mobetron EIORT unit (71% received 6 MeV), whereas our population was treated with 50 kV x-rays via INTRABEAM (6,18). Chen *et al* stratified their rate of distant metastasis-free survival by patients treated with salvage IORT to the primary tumor site vs. IORT to disease sites in the neck, revealing 3-year distant metastasis-free survival of 61 and 30%, respectively. While 65% of the total patients in our study were metastasis-free for the duration of their follow up, due to small population size, we were unable to perform statistical analysis for distant metastasis-free survival by patients treated with salvage IORT stratified by site of delivery. There are recent studies investigating the potential immunotherapy role of IORT in preventing recurrence in breast and pancreatic cancers (19,20), thus larger prospective studies would be useful for analyzing locoregional recurrence and distant metastasis in HNC patients who received IORT in the salvage setting.

Due to the small population size and the fact that six patient pathology reports were missing surgical margin data, we were unable to analyze outcomes as they pertain to surgical margin status. This limitation is relevant because multiple studies found that positive microscopic margins decreased in-field control when compared to negative margins (5,17). For instance, Chen *et al* found that in-field control was improved with negative margins compared to positive margins at 82% vs. 48% at 3 years (17).

Our study analyzed data from patients who received relatively low doses of IORT compared to that of other

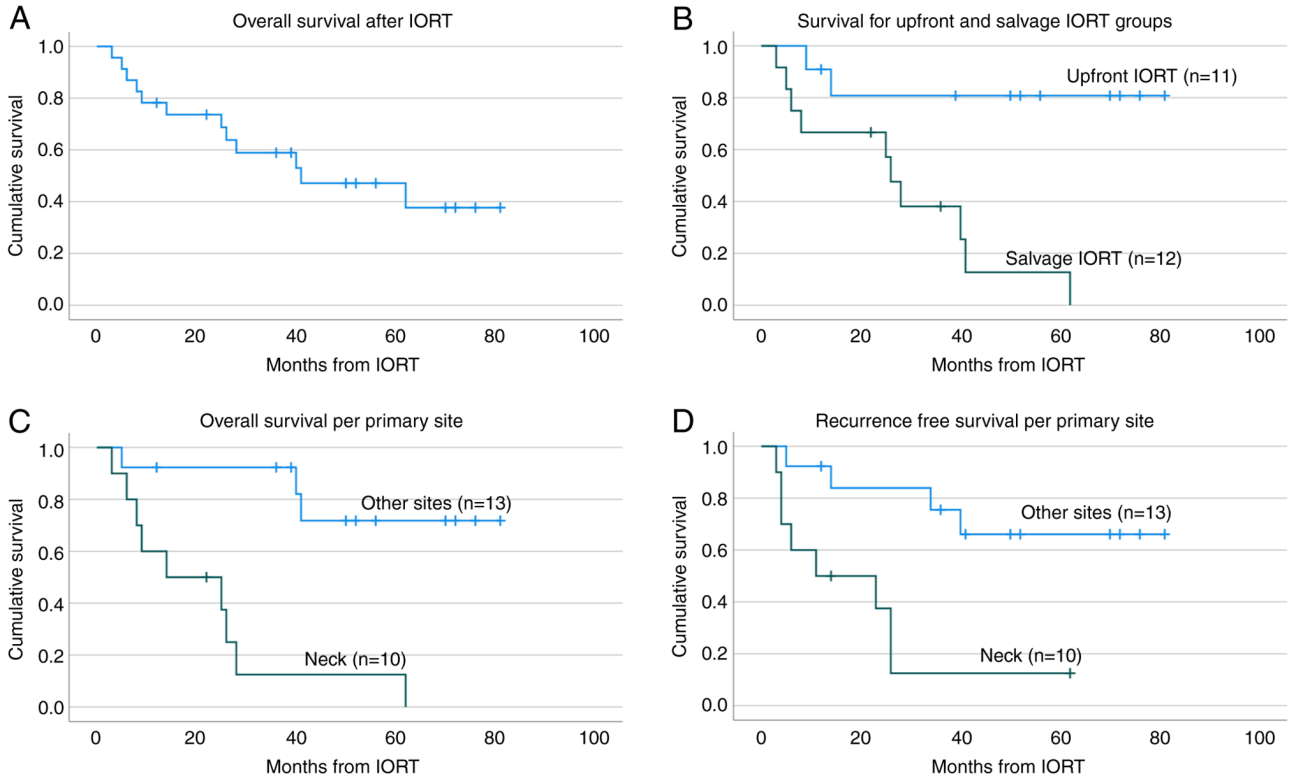

Figure 2. (A) K-M curves showing overall survival. (B) K-M curves showing survival in patients who received upfront vs. salvage IORT. (C) K-M curves showing survival per original disease site; other sites include parotid (n=11), tongue (n=2) and ear (n=1). (D) K-M curves showing recurrence free survival per original disease site. K-M, Kaplan-Meier; IORT, intraoperative radiation therapy.

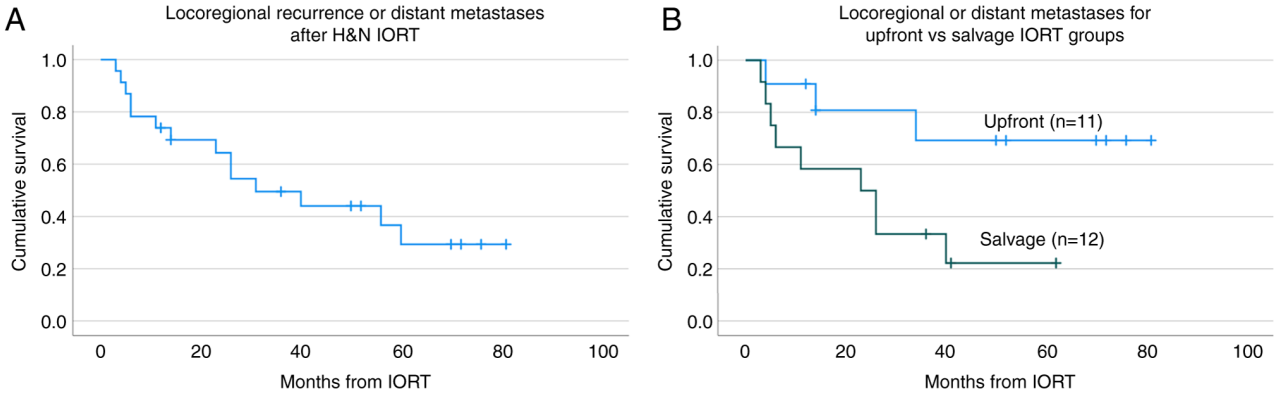

Figure 3. Local-regional control and incidence of distant metastases after IORT. (A) Overall incidence of local-regional recurrence or distant metastasis. (B) Incidence for upfront vs. salvage IORT. H&N, head and neck; IORT, intraoperative radiation therapy.

studies discussed, even after applying dose-rate correction factors (median dose 7.5 Gy, 8.57 Gy with dose-rate correction, compared to median dose range of 15-20 Gy, respectively) (5,17). Zeidan *et al* reported on data from a cohort of individuals who received 15 or 20 Gy IORT doses in the salvage setting and had a greater 3-year OS survival compared to our study (48% vs. 38%, respectively), but had 27% of study participants with toxicity, 7% with vascular toxicity and 6% with osteoradionecrosis, whereas our study had 9% toxicity, none with vascular toxicity or osteoradionecrosis. Chen *et al* reported a relatively lower median dose of 15 Gy, which is similar to that of our study median dose for those receiving salvage IORT, and they concluded that they had acceptable rates of toxicities. Toita *et al* report severe late complications with single IORT doses greater than 20 Gy (21). Further data are needed to explore this pattern suggestive of dose-dependent IORT-related toxicity.

Since most patients in the study had received radiation therapy prior to IORT, there is no meaningful way to analyze adverse effects from IORT. However, only one patient experienced protracted wound healing, and none of the patients in the study developed evidence of adverse events at the IORT site such as osteoradionecrosis, bone fracture or carotid blowout after receiving IORT. The fact that this study population experienced minimal complications after IORT points toward IORT at median dose of 7.5 Gy (8.57 Gy with correction) being

a safe modality for treating individuals with HNC, regardless of prior radiation to the site.

In conclusion, while overall survival for locally advanced or recurrent HNC is limited, the results of our retrospective study on patients with locally advanced and recurrent HNC treated with IORT show that IORT using INTRABEAM 50kV x-ray is a safe modality in this population with overall survival data comparable to that of published IORT studies. Prospective multi-center studies would be needed to further assess effect of IORT on overall survival, locoregional recurrence, and distant metastasis in the salvage setting.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CC and TR designed the study and created the outline for the manuscript. CC and SG performed the statistical analysis. CC and SG confirm the authenticity of all the raw data. CC generated Tables I and II. SG generated Figs. 1-3. CC, SG, BL, AB and TR analyzed and interpreted the data. BE, AS and WS acquired and interpreted the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The institutional review board (IRB #214428) at Loyola University Chicago approved the present study. No consent was required as this was a retrospective study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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