Original paper

Cesium-131 brachytherapy in high risk and recurrent head and neck cancers: first report of long-term outcomes

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Abstract

Purpose: The feasibility and efficacy of re-irradiation using contemporary radiation techniques to treat recurrent head and neck cancer has been demonstrated but the role of brachytherapy is unclear. Here we describe the use of ^{131}Cs brachytherapy with concurrent salvage surgery in 18 patients.

Material and methods: Eligible patients underwent maximal gross resection of the tumor with implantation of brachytherapy seeds delivering a minimum dose of 80 Gy to the tumor bed. Rates of overall survival, locoregional progression free survival, disease-free survival, and radiation-induced toxicity were analyzed.

Results: Retrospective Kaplan-Meier analysis shows median overall survival was 15 months and disease free survival was 12 months. Two patients developed grade 3 toxicity; all other complications were grade 1-2 with no grade 4 or 5 complications.

Conclusions: Compared to prior literature, our study shows comparable rates of survival with a decreased rate of radiation-induced toxicity.

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Key words: ^{131}Cs, brachytherapy, head and neck cancer, recurrence.

Purpose

Locoregional recurrences (LRR) of head and neck (HN) cancers are common and are difficult to treat. Progression of disease following recurrence is rapid, resulting in significant morbidity and mortality [1, 2, 3, 4, 5]. Optimal treatment of LRR is not been clearly defined due to complex factors, such as previous radiation (RT) treatment, tumor recurrence site, and performance status. Surgical resection of LRR is usually considered the standard of care [6, 7, 8, 9, 10, 11]. However, resection can be complicated by anatomic proximity to critical structures and primary treatment effects. In addition, salvage surgery alone has suboptimal outcomes for LRR of HN cancer with reported 5-year overall survival (OS) ranging from 11-39% and grade ≥ 3 complications ranging from 5-48% [12, 13, 14]. For unresectable tumors, chemotherapy (CT) or salvage external beam radiation therapy (EBRT) is considered, although response rates are poor with majority of patients dying within months [15].

Historically, salvage RT has been avoided in previously irradiated patients due to concerns about intolerable toxicity, including cerebrovascular accidents, carotid rupture, and skin and spinal cord necrosis [16]. Recent studies have shown the feasibility and effectiveness of re-irradiation using contemporary treatment techniques and delivery methods [17]. Despite this, there is no consensus on practical clinical and technical guidelines for the treatment of recurrent head and neck cancers.

Brachytherapy has been shown to be a promising treatment modality in the treatment of recurrent head and neck cancer achieving excellent local control even in the unresectable setting to deliver curative doses [18, 19, 20, 21]. Unlike EBRT, brachytherapy is able to deliver a high-localized dose with relative sparing of critical normal tissues due to rapid tissue falloff [22]. Although a high rate of local tumor control with limited morbidity can be achieved with brachytherapy [23, 24, 25, 26], there is no consensus about the role brachytherapy for LRR in HN cancers. Recognizing the need for further investigation, we initiated a program of salvage surgery with intraoperative brachytherapy using ^{131}Cs implants, a novel radioisotope with unique radiobiologic and dosimetric properties. Here we describe the incidence of radiation-induced

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toxicity, locoregional control (LRC), and OS in the first 18 patients (20 implants) undergoing ^{131}Cs implantation for recurrent head and neck cancer.

Material and methods

The study was an IRB approved retrospective analysis of patients treated with ^{131}Cs brachytherapy in HN cancers (#0511008245).

Patient and tumor characteristics

Patients that were included were recurrent biopsy-proven HN cancers, patients with a new cancer of the HN arising within previously irradiated fields or patients without prior RT but refused EBRT at the initial consultation. None of the patients had evidence of active distant metastatic disease (DM).

Surgery

A multidisciplinary team of radiation oncologists, medical oncologists, and HN surgeons coordinated patient care and evaluated patients prior to treatment. If the recurrent tumor was deemed resectable, a gross total resection of the tumor with implantation of the tumor bed with brachytherapy seeds was attempted (Figure 1). Immediate reconstruction was performed by a plastic surgeon if necessary.

Intraoperative brachytherapy

In patients who underwent resection, ^{131}Cs brachytherapy seeds were implanted at 0.5-1 cm distance, making sure that the tumor bed was covered by 80 Gy at 0.5 cm using a nomogram created in Variseed (Varian Medical System, Palo Alto, CA, USA) [27]. Median seed activity was 2.4 U (0.5 mCi/s). Median seed air kerma strength was 2.4 U (3.77 mCi apparent activity). Post implant dosimetry was analyzed using BrachyVision software (Varian Medical Systems, Palo Alto, CA, USA). The dosimetry and exposure rate have been previously reported by our institution in a prior study, with excellent dosimetric coverage and acceptable exposure rate to treating physicians and staff [23].

Briefly, after the resection of the tumor that needs to be implanted, the tumor bed (Clinical Target Volume-CTV) is identified and a ^{131}Cs plaque (Figure 1) is placed on the tumor bed (planer implant). The implant is placed so that it covers the entire tumor bed and an additional 0.5 cm around the tumor bed. This means that V_{100} (volume of CTV receiving 100% prescribed dose) is at 100%. In addition, D_{90} (dose going to 90% clinical target volume) is also at least 100% of the prescription dose in all implants. As mentioned previously, our prescription dose was 80 Gy. This technique of ^{131}Cs implant was performed as an open surgical procedure.

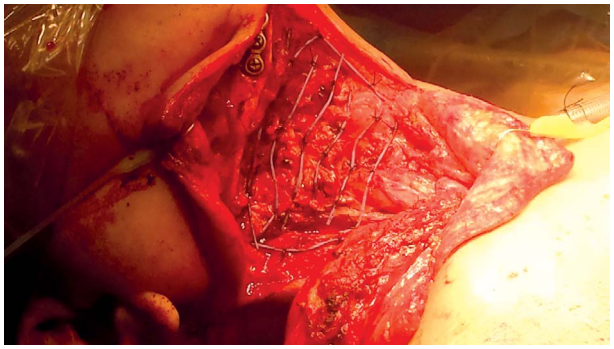

Fig. 1. Implantation of tumor bed with ^{131}Cs mesh

Follow-up

All patients were evaluated every 1-2 months by a radiation oncologist, medical oncologist, and/or a head and neck surgeon for the first 12 months, followed by evaluation every 3-4 months thereafter. Recurrence was evaluated by clinical examination and confirmed by contrast CT and/or FDG-PET.

Toxicity assessment

Acute toxicity and late complications were assessed retrospectively by reviewing all charts. All symptoms and complications that were documented in patient records during and following surgical resection with brachytherapy seed placement were recorded. Toxicity grading was according to the Radiation Oncology Toxicity Group criteria.

Statistical methods

Analysis was performed for toxicity, OS, locoregional progression-free survival (LRPFS), and disease free survival (DFS). The efficacy end points (OS, DFS, and LRC) were calculated from the date of the start of implantation to the date of the event. For OS, an event was death by any cause. For locoregional progression, an event was recurrence at the implantation site or development of regional node metastasis. For DFS, an event was locoregional failure, distant metastases, or death from another cause. Kaplan Meier analysis of OS, LRPFS, and DFS at 6, 12 and 18 months was performed. Toxicity was analyzed in a descriptive manner. SPSS software (IBM Corp. Armonk, NY, USA) was used for the statistical analysis.

Results

Between 2010 and 2013, a total of 18 patients with 20 implants were treated with surgical resection and ^{131}Cs brachytherapy. All patients were evaluated preoperatively with a history and physical examination, routine hematology and chemistry laboratories, axial imaging of the head and neck, and chest radiography. All patients were assessable for toxicity and overall efficacy.

Squamous cell carcinoma (SCC) was the most common histology (12/18). All but one patient had a history of prior radiation in the area of tumor recurrence. Prior definite EBRT dose prescription ranged from 50-70 Gy. One patient had gross residual disease following surgical resection. Two patients had microscopic margins positive for tumor, which the remaining patients had surgical margins free of tumor. Two patients underwent an addi-

tional surgical resection and brachytherapy implantation 2 months and 5 months later for local recurrence that developed outside the treatment volume. Thirteen patients had previous LRR treated with surgical salvage therapy. Patient characteristics are shown in Table 1.

All patients were implanted with ^{131}Cs seeds. The prescribed median dose was 80 Gy 0.5 cm from the implant (range 80-100 Gy). This was the total lifetime dose from the implant. All brachytherapy implants were permanent except in one patient, in which the seeds were removed after 39 days. Dose volume histograms (DVH) of two representative patients are shown in Figure 2. As shown in the figure, the most important and critical normal structure was the spinal cord, which received minimal radiation scatter.

Two patients developed grade 3 toxicity; all other complications were grade 1-2. No grade 4 or 5 complications were observed. The most common complications were dermatitis and hoarseness. Severe complications such as massive hemorrhage or cardiovascular accidents did not occur. A summary of the toxicity is shown in Table 2.

With a median follow-up of 38 months (total range 1-44 months), 11 patients developed another LRR of head-

Table 1. Patients characteristics

Patient/Age/Gender	Primary tumor site	Histology	Recurrence site/Implant site	Prior external radiation
1/69/M	Right buccal mucosa	SCC	Submental node/Submental region	Yes, post-op RT, full dose RT
		SCC	Right chin/Right chin subcutaneous	Yes, post-op RT, full dose RT
2/22/F	Left anterior 1/3rd tongue	SCC	Right neck/Right neck	Yes, CRT, 68 Gy
3/60/F	Soft palate	SCC	Residual disease on PETCT encasing carotid/Right neck implant with gross residual disease after resection	Yes, CRT, full dose RT
4/75/F	Right parotid	SCC	Right parotid/Right parotid bed	Yes, post-op RT, 63 Gy
5/77/M	Right parotid	Merkel cell carcinoma	Right preauricular node/Right neck	Yes, post-op RT, 63 Gy
6/82/F	Right hard palate	SCC	Bilateral neck nodes/Bilateral neck	Yes, post-op CRT, full dose
7/71/M	Left nasal cavity	Carcinosarcoma	Nasal cavity/Tumor bed after endoscopic resection	Yes, prior brain post-op radiation × 2 for resected tumors
8/88/M	Chest wall	SCC	Supraclavicular/Tumor bed after resection	Yes, post-op RT, 50 Gy
9/68/F	Left neck and parapharyngeal region	High grade sarcoma	Left neck/Left neck tumor bed	Yes, prior mantle radiation for Hodgkin's lymphoma
10/74/M	Right temporal region	Merkel cell carcinoma	Right zygoma/Tumor bed	Yes, post-op RT, 60 Gy
			Right parotid	Yes, post-op RT, 60 Gy
11/71/M	Left tonsil	SCC	Patient refused XRT after surgery/Left neck implanted	No, prior RT
12/66/F	Left maxilla	Osteosarcoma (RT induced)	Skull base/Tumor bed	Yes, post-op RT, 63 Gy
13/69/F	Left hard palate	SCC	Left neck node/Neck tumor bed	Yes, post-op RT, 54 Gy
14/83/F	Right maxilla with metastatic, right neck node	SCC	Right neck and parotid/Right neck	Yes, post-op RT, full dose RT
15/68/M	Nasopharynx	Mucoepidermoid carcinoma	Nasopharangeal tumor/Nasopharynx bed	Yes, CRT, full dose RT
16/70M	Left neck	SCC	Left neck nodes/Left neck	Yes, post-op RT, 63 Gy
17/62/M	Tongue	SCC	Base of tongue/Base of tongue tumor bed	Yes, 66 Gy
18/46/F	Piriform sinus SCC	SCC	Hypopharyngeal/Right neck	Yes, post-op RT, full dose RT

Full dose RT – RT given at outside institution, no definite dose available but documents suggesting full dose RT, post-op RT – post-operative radiation therapy, CRT – chemotherapy plus radiation therapy, SCC – squamous cell carcinoma

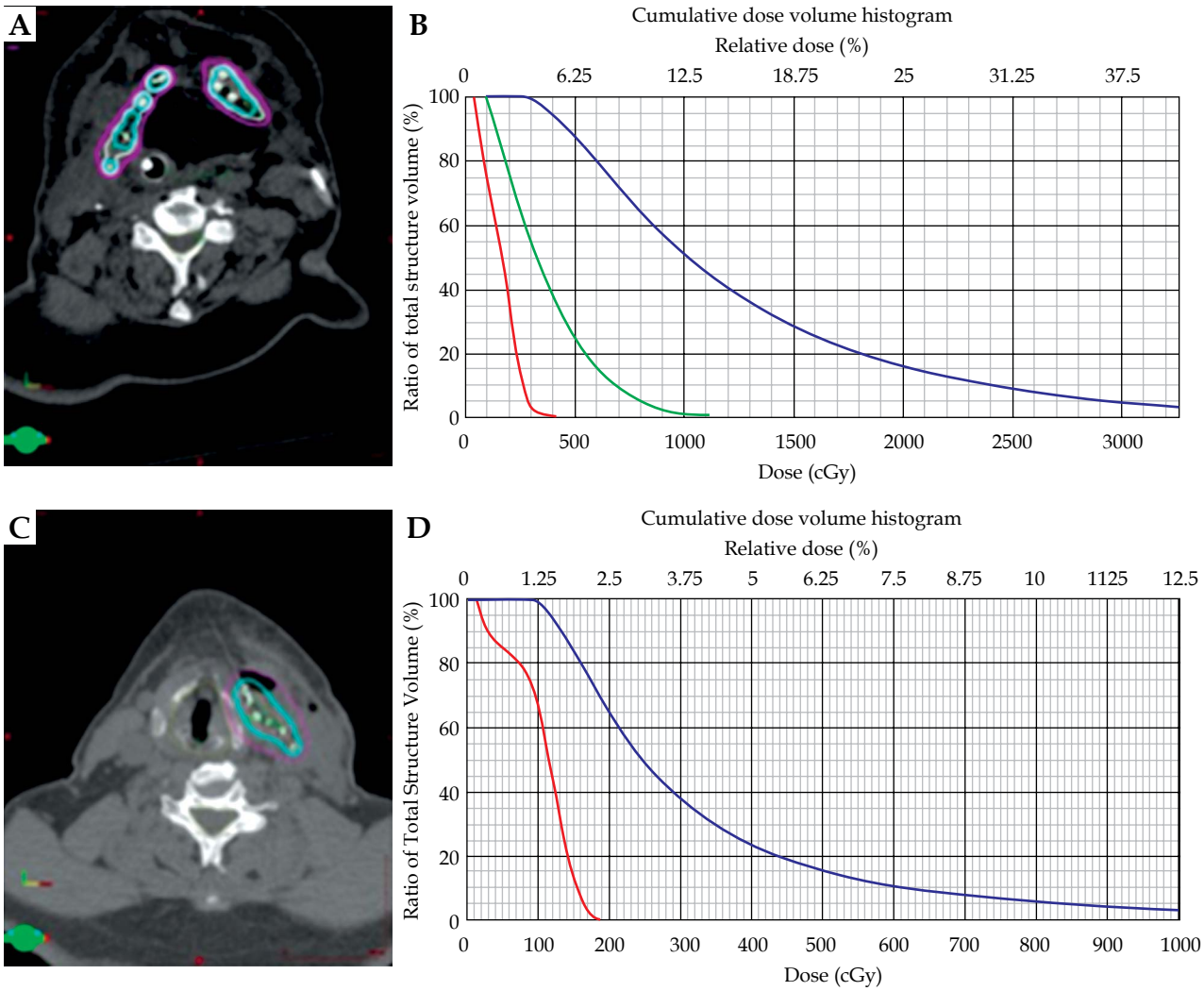

Fig. 2. A) Implant from patient #17 with **B)** dose volume histograms (DVH). Maximum esophagus and spinal cord dose was 22.26 Gy and 19.26 Gy, respectively. **C)** Implant from patient #13 with **D)** DVH. Maximum larynx, esophagus, and spinal cord dose was 53.43 Gy, 12.68 Gy, and 4.24 Gy, respectively

Table 2. Summary of toxicity due to brachytherapy and surgical resection

Toxicity	Grade				
Acute	1	2	3	4	5
Mucositis	2	0	0	0	0
Dermatitis	3	1	0	0	0
Hearing loss	0	1	1	0	0
Xerostomia	2	0	0	0	0
Dysphagia	2	0	0	0	0
Edema, larynx	0	1	1	0	0
Hoarseness	2	2	0	0	0
Fistula	2	1	0	0	0
Nasal cavity/Paranasal sinus reactions	1	0	0	0	0
Dyspnea	0	1	0	0	0

Table 3. Summary of clinical status

Patient	Clinical follow up		Resection margin	Local recurrence	Distant metastasis	Time to failure (months)
	Status	Time (months)				
1	DWD	24.33	R0	Y	Y (lung)	10.3
2	DWD	16.23	R0	Y	N	5.27
3	DWD	5.97	R0	Y	N	0.6333
4	ADF	43.43	R2	N	N	–
5	ADF	44.37	R0	N	N	–
6	DWD	2.77	R0	Y	N	1.5333
7	DDF	14.43	R0	N	N	–
8	DWD	12.27	R0	N	Y (brain)	11.87
9	ADF	38.67	R0	N	N	–
10	DWD	14.50	R0	Y	Y (node)	3.83
11	ADF	24.30	R1	N	N	–
12	DWD	8.80	R0	Y	Y (bone)	1.9
13	DWD	12.20	R0	N	Y (lung)	1.4
14	AWD	29.27	R0	Y	N	14.1
15	LTF	0.97	R0	N	N	–
16	DDF	1.00	R0	N	N	–
17	AWD	12.17	R1	Y	N	5.2
18	DWD	4.93	R0	N	Y (Node)	1.23

DWD – dead with disease, DDF – dead, disease-free, AWD – alive with disease, ADF – alive, disease-free, LTF – lost to follow-up, N – no

and-neck cancer, including the patient who had gross residual disease remaining after attempted surgery. In 6 of these 11 cases, the failure was locoregional and in 4 patients, it was isolated distant failure. One patient was found to have simultaneous locoregional and distant progression of disease. A summary of clinical follow-up of all patients is shown in Table 3.

The median OS was 15 months and DFS was 11 months. The 6, 12, and 18 month OS rate in this study was 77%, 71%, and 45% (Figure 3). The 6, 12, and 18 month LRPFS rate in this study in patients was 69%, 62%, and 52% (Figure 4). The 6, 12, and 18 month DFS rate in this study was 57%, 45%, and 37% (Figure 5).

For patients with SCC and had received prior radiation, median OS was 12 months, LRFS is 14 months and disease free survival was 5 months (Table 4). The 6, 12, and 18 month OS rate for these patients was 53%, 53%, and 21%. The 6, 12, and 18 month LRPFS rate for these patients was 65%, 52%, and 26%. The 6, 12, and 18 month DFS rate in these patients was 47%, 24%, and 9%.

Discussion

Our results demonstrate that brachytherapy with ^{131}Cs as an intraoperative/adjuvant to surgical resection is feasible with low rates of acute toxicity. This is the first study investigated at the outcomes and toxicities of ^{131}Cs permanent implants for head and neck cancer.

For recurrent, operable head and neck cancer, salvage surgery is the treatment of choice [9]. Surgery before re-RT and chemotherapy for recurrent squamous-cell head

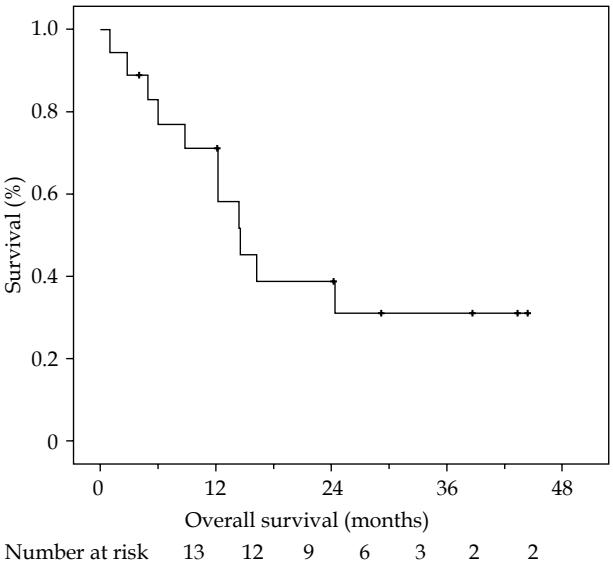

Fig. 3. Overall survival in entire patient population (n = 18)

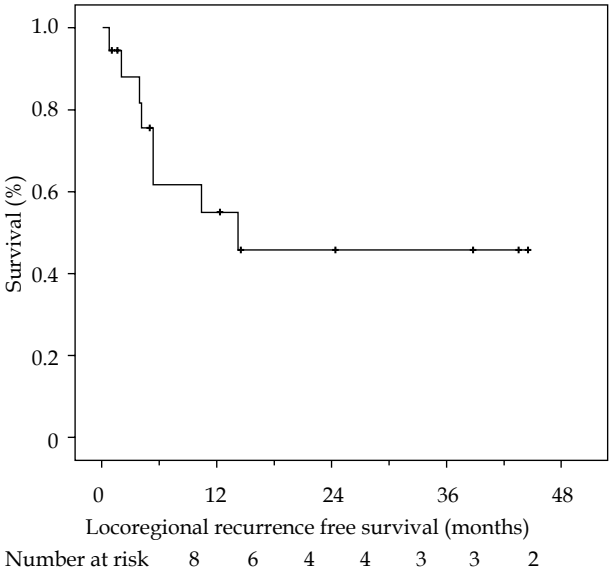

Fig. 4. Locoregional progression free survival in entire patient population (n = 18)

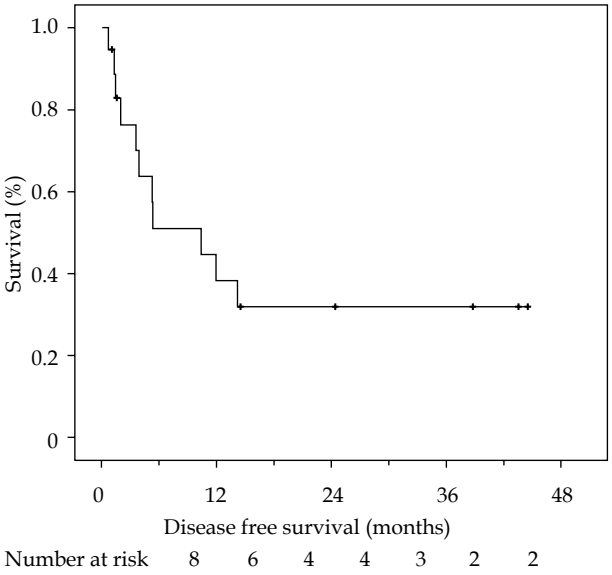

Fig. 5. Disease free survival for entire patient population (n = 18)

Table 4. Patients with squamous cell carcinoma (SCC) and prior radiation that received ^{131}Cs implant

N	Median follow-up	Local control	Distant metastasis	Median time to failure
10	12.23 months	5/10 (50%)	4/10 (40%)	3.4 months

and neck cancer is an independent prognostic factor, predicting improved LRPFS, progression-free survival (PFS), and OS [24]. Additional studies for surgical salvage with re-RT and/or CT report LRC rates ranging from 15-60% and overall survival 5 year survival ranging from 36-60% [28, 29, 30, 31]. The predominant pattern of failure in the salvage resection of head and neck cancers is local and regional recurrence [11, 32, 33, 34, 35]. A review of 22 studies by Goodwin *et al.* of patients who underwent surgical salvage found that the overall 2 year disease-free survival was 51.1%, with individual studies reporting 75-90% of these failures due to recurrence at the primary sites or regional nodes only [14, 36, 37]. We were able to achieve comparable rates of locoregional control and survival in our study, supporting the viability of ^{131}Cs brachytherapy as an alternative adjuvant therapy following surgical salvage.

In patients who were able to receive surgical resection, brachytherapy has been used to improve local control and overall survival with reported 2 year local control ranging from 40% to 85%, and 2 year overall survival of 29% to 55% [17, 38, 39, 40]. Similar studies have investigated adjuvant brachytherapy for recurrent cancer using Ir-192 and I-125 based implants have shown benefit in improving LC [41, 42, 43]. Permanent I-125 implants have shown benefit in improving LC. Recently, Zhu *et al.* reported the use of I-125 brachytherapy in 19 patients as adjuvant to surgical salvage in patients with recurrent head and neck carcinomas [44]. The median LC was 24 months and the one-, two-, and three-year local control rates were 73.3%, 27.5%, and 27.5%, respectively. We report similar rates of LRC within a similar time period of 69%, 62%, and 52% at one, two, and three years, respectively, supporting the viability of interstitial ^{131}Cs brachytherapy as an alternative adjuvant therapy following surgical salvage.

In addition, ^{131}Cs has multiple favorable dosimetric properties compared to SBRT and ^{125}I. ^{131}Cs has a higher dose rate of 0.342 Gy/hr whereas ^{125}I has a dose rate of 0.069 Gy/hr, allowing for a greater dose to be delivered in a shorter period of time. This makes ^{131}Cs ideal for treating aggressive tumors like head and neck cancer. In addition, radiation exposure to the treating team is quite limited since > 95% radiation dose is delivered within 40-45 days after surgical resection. This ensures increased safety for treating physician and patient's family members. A study by our institution in a series of 28 patients who received Cs-13 implants for early stage lung and recurrent H&N cancer measured the radiation exposure to the treating physicians and staff and found that the exposure rate was acceptable [27].

Brachytherapy offers excellent local dose escalation within the tumor volume with steep dose gradients to minimize dose to the surrounding tissue, thus theoretically minimizing acute toxicity. In our study, there was a low rate of acute and chronic toxicity. This is consistent with studies that have investigated the use of brachytherapy for localized HN disease. Kupferman *et al.* reported in a study using ^{192}Ir and demonstrated early adverse events in 23% of patients with 3 patients experiencing grade 3/4 events [45]. Other studies have demonstrated grade 3/4 toxicities for head and neck brachytherapy from 7% to 26 % [24, 44, 45, 46]. We found similar rates of grade 3/4 events in our own series with two of our 18 patients having grade 3 toxicity. Compared to studies inves-

tigating adjuvant EBRT after surgery, our series demonstrated lower rates of acute toxicity. Studies involving re-irradiation using adjuvant EBRT report complication rates ranging from 11 to 50% [29, 47, 48, 49].

Our study has several important limitations. First, it is based on a nonrandomized heterogeneous cohort of patients from a single institution; therefore, definitive causal inferences should not be drawn. Because toxicities were retrospectively determined based on chart review rather than prospectively collected, it is possible that not all complications were captured. Lastly, with a patient cohort of 18, a larger study with more patients is needed to fully assess the long-term complications associated with brachytherapy implantation. Nevertheless, we show here that ^{131}Cs brachytherapy may play a beneficial role in the treatment of recurrent head and neck cancer and warrants further study.

Disclosure

Isoray research funding.
Authors report no other conflict of interest.

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