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Clinical outcomes after local field conformal reirradiation of patients with retropharyngeal nodal metastasis

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Abstract

Background. We present our experience with retropharyngeal node reirradiation using highly conformal radiotherapy.

Methods. A retrospective screen of 2504 consecutively irradiated patients with head and neck malignancies between 2005 – 2015 identified 19 patients that underwent reirradiation for retropharyngeal node metastasis. Clinical and toxicity outcomes were assessed in these patients.

Results. Thirteen (68%) patients had squamous cell carcinoma. Eleven (58%) received conventionally fractionated intensity modulated radiotherapy (IMRT) or proton therapy, and eight (42%) received single- or hypo-fractionated stereotactic radiotherapy. Fourteen (74%) received chemotherapy. Median follow up was 14.7 months. The 1-year local control, locoregional control, overall survival, and progression free survival rates were 100%, 94%, 92%, 92%, respectively. Three patients (16%) experienced acute grade 3 toxicity and occurred in those treated with IMRT. There was no late grade ≥ 3 toxicity.

Conclusions. Retropharyngeal node reirradiation with conformal therapy is well tolerated and associated with excellent short-term disease control.

Introduction

Retropharyngeal (RP) lymph nodes are located in the buccopharyngeal fascia, posterior to the superior portion of the nasopharynx, and anterior to the arch of atlas. The RP lymph nodes directly drain the nasal cavity, nasopharynx, and the auditory tubes. The node of Rouviere is the most superior of the lateral group of RP nodes, can be involved in cancers of the nasopharynx, oropharynx, hypopharynx, and paranasal sinus, and metastasis to this location is a harbinger of poor prognosis¹.

Radiation therapy is often used to target RP nodes as definitive treatment for gross disease involvement or as a prophylactic measure in head and neck (HN) sites with predilection for RP nodal metastases. Elective irradiation to RP nodal basins in patients with high-risk primary sites result in exceptional locoregional control². Intensity modulated radiation therapy (IMRT) allows for the use of a simultaneous integrated boost technique with more selective and precise dose delivery to different organs and requires delineation of RP nodes as a clinical target. At our institution prophylactic doses of 54-57 Gy to the RP nodal basins (in the absence of gross involvement) are typically considered in patients with malignancies of the pharynx.

Patients with RP recurrences after radiation therapy can be salvaged by surgical resection. However, due to proximity of critical structures such as the carotid artery and prevertebral fascia, complete resection of tumor may be associated with a high risk of morbidity. RP node reirradiation is a potentially curative strategy and newer conformal techniques offer the potential of reduced toxicity. Currently, there is sparse clinical data on RP reirradiation outcomes making it difficult to decipher optimal management for these patients³. Studies including reirradiation of RP nodes are analyzed in aggregate with other head and neck

sites and the numbers are small. In this study we present our single institutional experience treating recurrent RP node disease with local field radiation therapy utilizing IMRT, proton beam therapy (PBT), head and neck stereotactic body radiation therapy (HN-SBRT), and gamma knife stereotactic radiosurgery (GK-SRS), evaluating clinical outcomes and treatment related toxicity.

Methods and Materials

Patients

This study was approved by the institutional review board and informed consent obtained from study participants. We queried the medical records of all patients from 2000 to early-2015 in our departmental database. Of the 2504 patients with HN malignancies previously irradiated from 2000 to early-2015, we identified a total of 26 patients that ultimately developed recurrences in the RP node basin and subsequently received reirradiation with curative intent. Of these, 6 patients were excluded for having multifocal recurrent disease including those with involvement of the oropharynx (n=3), nasal cavity (n=1) and skull base (n=2). One patient was excluded due to not completing the intended treatment. Patients with < 2cm direct extension to the adjacent nasopharynx or ipsilateral neck (n=5) were included.

Of the 19 patients, human papilloma virus (HPV)-status was available in only 4 samples (1 HPV positive) and therefore was not factored in further analyses. RP node recurrences were verified by biopsy and/or radiographic imaging. Diagnostic imaging obtained included magnetic resonance imaging (MRI), positron emission tomography-computed tomography (PET-CT), and/or computed tomography (CT).

After reirradiation, follow-up evaluations were performed at 3 months interval during the first year post-treatment, at 4 months interval between years 1 and 2 post-treatment, at 6 months interval between years 2 and 5 post-treatment, and annually thereafter according to institutional guidelines after reirradiation. As of 2013, these guidelines were formalized as part of our reirradiation protocol. Follow-up evaluation consisted of repeat history, symptom assessment, physical examination and imaging studies. Physical examination included nasopharyngolaryngoscopic exam by a staff radiation oncologist. Imaging studies included MRI, PET-CT scan, and/or CT at the discretion of the treating physician.

Treatment Planning

IMRT, HN-SBRT and PBT patients received a simulation CT scan with a custom head and neck mask. IMRT/volumetric arc therapy (VMAT) and HN-SBRT treatment plans were performed using the Pinnacle treatment planning system (Philips Healthcare, Fitchburg, WI). For HN-SBRT patients, 1-mm planning CT images were coregistered with planning MRI images, contrast-enhanced CT or PET-CT images in treatment position to delineate target and critical avoidance structures such as carotid vessels (**Figure 1A-C**). PBT plans were created using the Eclipse proton therapy planning system (Varian Medical Systems, Palo Alto, CA). Gamma Knife treatment plans were performed with the Leksell GammaPlan treatment planning system (Elekta, Stockholm, Sweden). For IMRT and PBT plans, contouring involved identifying the gross tumor volume with an 8 – 10mm circumferential margin designated as clinical target volume 1 (CTV 1). When the target volume abutted critical structures a reduced CTV1 margin was used (0 – 5mm), which was ultimately determined by the treating radiation oncologist. Intermediate and elective nodal doses were used sparingly and only with IMRT or PBT treatment plans.

IMRT was either delivered using a step-and-shoot technique or volumetric modulated arc therapy technology. Both techniques utilized multileaf collimation. Planning target volumes (PTVs) were generated by expanding the corresponding CTV by 3mm. Dose was prescribed to the PTV with the goal of >95% coverage.

PBT was delivered using a 2-field or 3-field passive scatter proton therapy or by active scanning intensity modulated proton therapy (IMPT). Beam angles were chosen for each plan to optimize target coverage while minimizing dose to OARs. Final optimization was performed accounting for range and isocenter shift uncertainties as previously reported⁴. We previously published the technical and planning methods of our IMPT experience⁴⁻⁶.

HN-SBRT treatment was delivered using the Varian TrueBeam STx system (Varian Medical Systems, Inc., Palo Alto, Ca) with high definition (2.5 mm) leaflets and planned using 2-3 arc VMAT technique with patients immobilized in a custom biteblock-mask-cushion system with image guided on-line setup correction as previously described⁷⁻⁹. HN-SBRT was delivered in 5 fractions every other day over 2 weeks.

GK-SRS was delivered using the Leksell Perfexion (Elekta, Stockholm, Sweden). On the morning of treatment, a rigid head frame was placed on patient under local anesthesia by the neurosurgeon and thin-slice (1-mm) gadolinium-enhanced MRIs (T1 sequence) were performed and then transferred to the Leksell GK treatment planning system for treatment planning. Treatment volumes (gross tumor with no PTV margin) were prescribed to the 50% isodose line with a mean dose of 17.5 Gy.

Data Analysis

Endpoints included local control (LC), locoregional control (LRC), progression free survival (PFS), and overall survival (OS) calculated from the end of radiation treatment using the Kaplan-Meier algorithm based on a first event analysis for all endpoints. For the purposes of this analysis, local recurrence was defined as persistence or recurrence in the treated RP disease, and regional recurrence as recurrence in any head and neck site (mucosal or nodal) exclusive of the treated RP nodes. Actuarial statistics for clinical outcomes were calculated using SPSS Statistics v. 23.0 (IBM Corporation, Armonk, NY). Toxicity was determined using the Common Terminology Criteria for Adverse Events (CTCAE v.4.0). Toxicity parameters were assessed at follow up and graded by the treating radiation oncologist.

Results

Patient and treatment characteristics

Table 1 summarizes patient, tumor and treatment characteristics. Of the 19 patients that received RP node reirradiation, 14 (74%) had isolated RP node recurrences, and 5 (26%) had RP node recurrences with limited direct extension to either the ipsilateral level 2A neck (n=3) or nasopharynx (n=2) (**Figure 2A - C**). Twelve (63%) patients were male. Initial primary sites included: tonsil (n=3), oral cavity (n=3), nasopharynx (n=3), nasal cavity (n=3), larynx (n=2), sinonasal (n=2), thyroid (n=1), parotid (n = 1), unknown primary (n = 1). The majority of patients (n=13) had squamous cell carcinoma (SCC). The non-SCC histologies included: nasopharyngeal carcinoma (n=3), sinonasal undifferentiated carcinoma (SNUC) (n=1), esthesioneuroblastoma (n=1), and medullary thyroid carcinoma (n=1).

The median time interval between first and second radiation courses was 40.2 months (range: 10.3 – 127.9 months). Reirradiation modalities were IMRT (n=7), HN-SBRT (n=6), PBT (n

= 4), and single fraction GK-SRS (n=2) (**Figure 3A – D**). Among the 5 patients with limited extension beyond the RP nodal basin, 3 received IMRT and 2 received HN-SBRT. The median dose/fractionation for IMRT, PBT and HN-SBRT were 66Gy/33 fractions, 45Gy/5 fractions delivered every other day, and 68Gy/33 fractions, respectively. The mean single fraction GK-SRS dose was 17.5 Gy prescribed to the 50% isodose line.

Fourteen (74%) patients received systemic therapy. One patient received induction, 13 received concurrent, and 3 received both induction and concurrent systemic therapy. Concurrent systemic therapy consisted of: cetuximab (n=7), cisplatin (n=3), and carboplatin (n=3). Induction systemic therapy consisted of: carboplatin/etoposide x 3 cycles (n=1), carboplatin/docetaxel x 3 cycles (n=2), and carboplatin/paclitaxel/cetuximab x 6 cycles (n=1).

Clinical Outcomes

The median follow up time after reirradiation was 14.7 months (range: 3.3 – 103.9 months). The 1-year LC, LRC, OS, and PFS rates for the entire patient cohort were 100%, 94%, 92%, and 92% respectively (**Figure 4A - D**). There were no local recurrences and 3 regional recurrences: posterior sinonasal cavity (n=1), ipsilateral supraclavicular node (n=1) and contralateral upper neck (n=1) outside of the reirradiation field. The patient with disease recurrence of the posterior sinonasal cavity was treated with GK-SRS for left-sided isolated RP recurrence from history of a multiply recurrent esthesioneuroblastoma status-post surgery and postoperative radiotherapy. This patient developed a recurrence 19.7 months after GK-SRS and was salvaged with HN-SBRT and currently displays no evidence of disease (NED). There was 1 distant recurrence involving the lung. This patient also had a regional recurrence. The median time to recurrence after reirradiation was 19.7 months (range 1.9 – 23.9 months). Of the 3

regional recurrences, 1 was treated with GK-SRS, 1 was treated SBRT, and 1 was treated with IMRT, and two (67%) did not receive chemotherapy.

Treatment Related Toxicity

A total of 35 physician reported toxicities events were identified (28 acute and 7 late). There were 3 acute G3 adverse events. There were no G4-5 events reported. All G3 acute adverse events were related to mucositis (n=3) requiring narcotics and interfering with oral intake, and occurred in patients treated with IMRT (43%; 3 of 7 patients treated with IMRT).

There were no $\geq$ G3 late toxicities. Of the 7 reported G1-2 late toxicities, xerostomia (n=5) was the most common event. One patient developed G2 trismus that was initially treated with 3D-CRT for supraglottic larynx cancer and reirradiated to the left RP node 7 years later with PBT. One patient previously treated with IMRT for nasopharynx cancer in 2001 and reirradiated with IMRT for a left RP recurrence 7 years later, developed mild asymptomatic radiation-induced left temporal lobe necrosis 2 years after reirradiation. Review of the reirradiation plan showed a dose of 20 Gy in 33 fractions in the area of radionecrosis. The original RT plan was not available. All 7 patients with late toxicities also had acute toxicities.

Treatment related toxicity data is summarized in absolute number of reported symptoms in

Table 2.

Discussion

Management of RP node recurrence after prior head and neck radiotherapy represents a therapeutic challenge. Historically, the use of surgery is preferred over reirradiation because of severe toxicity concerns with repeat high dose radiation (cumulative dose > 100 Gy) such as

severe fibrosis, dysphagia, xerostomia, carotid artery rupture, soft tissue necrosis and osteoradionecrosis¹⁰. Here, we demonstrate that use of highly conformal radiotherapy techniques for reirradiation of RP node recurrences offers excellent disease control with 1-year LC of 100% and LRC of 94%. Treatment was well tolerated and toxicity was limited to acute mucositis in 16% of patients. The majority of our patients received chemotherapy in some form, which may account for the favorable disease control.

Several studies have investigated the impact RP nodal metastasis on disease outcomes¹¹⁻¹³. Gunn et al. found that RP node involvement in patients with oropharyngeal cancer was associated with worse 5-year LC (79% vs 92%), nodal control (80% vs. 93%), recurrence-free survival (51% vs. 81%), and OS (52% vs. 82%) ($P < 0.001$ for all)¹⁴. Dirix et al. demonstrated patients with RP lymphadenopathy at the time of diagnosis had higher rates of regional recurrence (45% vs. 10%, $p = 0.004$) and lower disease specific survival (38% vs. 58%, $p = 0.03$)¹⁵. Harada et al. showed that patients with hypopharyngeal cancer and RP nodal involvement had significantly worse 2-year OS (0% vs. 68%, $p < 0.01$) and 2-year cause specific survival (0% vs. 74%, $p < 0.01$) than those with no RP node involvement¹⁶.

Although Garden et al. showed that RP node recurrence in electively treated patients is rare¹⁷, in those who do recur, evidence suggests surgical salvage of RP node metastasis improves tumor control and survival¹⁸. Depending on the location of the recurrence, surgical resection can be accomplished by a transcervical or transmandibular approach. The maxillary swing operation, an open procedure, has been defined as an effective approach to resect tumor in the RP space because it provides superior surgical access and an ability to resect the parapharyngeal space *en bloc* with the pharyngobasilar fascia^{18,20,21}. However, open surgical

procedures are associated with multiple morbidities including surgical site infections, cranial nerve palsies, palatal fistula, trismus, cerebrospinal fluid leak, velopharyngeal incompetence, choanal stenosis, dental malocclusion, and poor wound healing related to atrophy of surgically involved soft tissues^{19,22,23}. Chan et al. analyzed 82 patients with RP recurrences after definitive radiation therapy for nasopharyngeal carcinoma and subsequently salvaged with the maxillary swing approach¹⁸. The 5-year actuarial tumor control and overall disease free survival (DFS) of patients were 79.6% and 59%, respectively. Quality of life assessment in these patients showed that the most significant side effects were palatal fistula (4.3%), severe trismus (13.5%), and osteoradionecrosis (16.2%, attributed to a combination of primary radiotherapy and exposed bone after surgical procedure)²⁴. Endoscopic transnasal surgery and transoral robotic surgery (TORS) are alternatives to open approaches in select cases but require resection of the nasopharynx to expose the parapharyngeal space, which may lead to unnecessary risks of carotid artery damage, middle ear effusion and hearing damage. In patients with isolated RP node recurrences, routine resection of the nasopharynx may incur unnecessary risks.

Highly conformal radiotherapy techniques have reinvigorated a reassessment of curative intent reirradiation as an alternative treatment option for selected patients with HN cancer²⁵⁻³⁰. However, for those with RP recurrences, the clinical evidence supporting use of reirradiation in the literature is sparse^{25,28,29}. In the present study, we demonstrated excellent local control after isolated RP node reirradiation with no significant differences among single-, hypo- and conventionally-fractionated approaches, suggesting an adequate biologic effective dose can be achieved with stereotactic radiation therapy using 16-18 Gy in a single fraction or 40-45 Gy in 5 fractions, confirming findings from other head and neck stereotactic radiation

therapy studies evaluating the optimal dose/fractionation for recurrent head and neck tumors^{27,30}.

The incidence of acute grade 3 (G3) toxicities was low (~11% of all acute toxicities) with no acute G4-5 toxicities, and late toxicity was limited to G1-2 events. The majority (84%) of our patients had non-nasopharyngeal cancers and likely received less total radiation dose to the nasopharyngeal/RP region, which may partially account for the lower rates of toxicity in this cohort compared to reported HN reirradiation rates^{31,32}. Our previously reported institutional HN reirradiation data showed 1- and 2-year $\geq$ G3 toxicity rates of 19.9% and 32% (for IMRT) and 16.5% and 27.1% (for PBT), respectively, and that retreatment volume was associated with toxicity rates^{26,28}. In patients with CTV1 volumes <50 cc the 1-year G3 toxicity rates were significantly lower (11.6% for IMRT; and 8.7% for PBT), and similar to toxicity rates presented here. In our current study, all 3 acute G3 toxicity events were mucositis and occurred in IMRT patients (n=7; representing 43% of IMRT patients) and none in those who received PBT, HN-SBRT, or GK-SRS, suggesting increased conformality and lower integral dose are advantageous in the reirradiation setting.

This study has several limitations, including inherent biases of a retrospective analysis, limited patient number, and a relatively short follow up period. In addition, the patient population includes tumors of different histologies and the use of varying induction and concurrent chemotherapy regimens which can impact clinical outcome. A previous benchmark study by Gunn et al. evaluated a cohort of nearly 1000 patients with oropharyngeal SCC and the incidence of radiographically involved RP node was ~10%¹⁴. In our database of 2504 head and neck radiotherapy patients, approximately 1% (26 patients) were found to have a RP recurrence

in a previously irradiated field. These findings are consistent with our prior observations that recurrence in electively treated regions is extremely rare¹⁷ and support our institutional approach of routine elective RP nodal irradiation in patients with pharyngeal and posterior nasal cavity primaries. Physician reported assessment of adverse events can vary in incidence and severity, and parsing out the influence of prior treatment is a challenge. Evaluating G3 or higher toxicities help mitigate some of these concerns. Conversely, the strength of this study is a unique assessment of a homogeneous patient population reirradiated to the RP nodal basins using highly conformal modalities.

Conclusions

Conformal local field reirradiation in patients with RP nodal recurrences offers excellent local control and survival at 1 year and is well tolerated. The use of limited field reirradiation may provide an alternative to surgical salvage strategies and appears associated with a favorable toxicity profile. Longer-term follow up and greater patient numbers are needed to confirm clinical outcomes and late effects of RP node reirradiation. Due to the rarity of the clinical presentation, a large prospective randomized controlled trial would be difficult to implement.

Figure Legend

Figure 1. Treatment planning procedure for patients treated with HN-SBRT. (A) Representative axial slice of planning CT scan, 1mm slice. The right RP tumor and carotid vessels are difficult to visualize. White arrow identifies the right RP tumor. Hollow red circle is isocenter. (B) Coregistration of the planning CT scan with a volume MRI in treatment immobilization position. Visualization of the tumor (white arrow) and contralateral carotid vessel (red arrow). Hollow red circle is isocenter. (C) Final HN-SBRT treatment plan with isodose lines. Right carotid artery (outlined in light blue) is receiving < 8 Gy.

Figure 2. Patterns of disease presentation of patients included in analysis. (A) Isolated right retropharyngeal node metastasis, red circle. (B) Retropharyngeal node metastasis with extension to the ipsilateral carotid space and level 2A, dashed line. (C) Retropharyngeal node metastasis with extension to the ipsilateral nasopharynx, dashed circle.

Figure 3. Radiation treatment plan representative images. (A) IMRT plan. (B) PBT plan. (C) HN-SBRT plan. (D) GK-SRS plan.

Figure 4. Clinical outcomes. (A) Local control (LC) for entire patient cohort (n = 19). (B) Locoregional control (LRC) for entire patient cohort (n = 19). (C) Progression free survival (PFS) for entire patient cohort (n = 19). (D) Overall Survival (OS) for entire patient cohort (n = 19).

Table 1. Patient, tumor, and treatment characteristics. All patient, tumor, and treatment characteristics are reported in absolute numbers. Abbreviations: SCC, squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma; IMRT, intensity modulated radiation therapy; HN-SBRT, head and neck stereotactic body radiation therapy; PBT, proton beam therapy; GK-SRS, gamma knife stereotactic radiosurgery; Gy, gray;.

Table 2. Complete toxicity data. All adverse events are reported in absolute numbers.

Abbreviations: No., number; IMRT, intensity modulated radiation therapy; HN-SBRT, head and neck stereotactic body radiation therapy; PBT, proton beam therapy; GK-SRS.

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Patient Characteristics	No. of Patients
Gender	
Male	12
Female	7
Site of Initial Disease	
Tonsil	3
Oral Cavity	3
Nasopharynx	3
Nasal Cavity	3
Larynx	2
Sinonasal	2
Thyroid	1
Parotid	1
Unknown Primary	1
Histology	
SCC	13
Non-SCC	6
Nasopharyngeal Carcinoma (All WHO III)	3
SNUC	1
Esthesioneuroblastoma	1
Medullary Thyroid	1
Radiation Modality	
IMRT	7
HN-SBRT	6
PBT	4
GK-SRS	2
Median/Mean radiation dose, Gy (range)	
IMRT	66 (66-69.96)
HN-SBRT	45 (40-47.5)
PBT	68 (66-70)
GK-SRS	17.5 (17-18)
Chemotherapy	
Any Systemic Therapy	14
No Systemic Therapy	5
Induction Only	1
Concurrent Only	10
Induction + Concurrent	3

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Treatment Related Toxicity	No. of All Adverse Events	No. of IMRT Adverse Events	No. of PBT Adverse Events	No. of HN- SBRT Adverse Events	No. of GK- SRS Adverse Events
Total	35	18	5	10	2
Acute	28	15	4	9	0
Late	7	3	1	1	2
Acute Toxicity Grade					
<3	25	12	4	9	0
≥3	3	3	0	0	0
Acute Grade 3 Toxicity Type					
Mucositis	3	3	NA	NA	NA
Other	0	0	NA	NA	NA
Acute Grade 3 Toxicity by Modality					
IMRT	3	NA	NA	NA	NA
HN-SBRT/PBT/GK-SRS	0				
Acute Grade <3 Toxicity Type					
Mucositis	4	2	0	2	0
Dysphagia	3	3	0	0	0
Odynophagia	3	0	0	3	0
Xerostomia	5	1	1	3	0
Pain	3	2	1	0	0
Dermatitis	6	3	2	1	0
Weight Loss	1	1	0	0	0
Late Toxicity Grade					
<3	7	3	1	1	2
≥3	0	0	0	0	0
Late Grade <3 Toxicity Type					
Xerostomia	5	2	0	1	2
Trismus	1	0	1	0	0
Temporal Lobe Necrosis	1	1	0	0	0

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