Adult Head and Neck Rhabdomyosarcoma: Management, Outcomes, and the Impact of IMRT on Locoregional Control

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Running Title:
Adult Head and Neck Rhabdomyosarcoma

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Abstract

Purpose:

Only 9% of adult Rhabdomyosarcomas (RMS) present with primary disease in the head and neck (HNRMS). Management is often extrapolated from the pediatric experience where prognosis is better but treatment imperatives differ. We report management and outcomes of adult HNRMS treated over 3 decades.

Methods:

Adult HNRMS treated from 1984-2017 were reviewed. HNRMS were categorized as embryonal/alveolar (E/A) or pleomorphic (P). Standard management was as follows: E/A-HNRMS were treated with neoadjuvant chemotherapy, definitive chemoradiotherapy (CRT), and then maintenance chemotherapy. P-HNRMS were generally treated with surgery +/- radiation. IMRT was adopted from 2005 onward.

Results:

Fifty-eight patients were eligible; median age was 32 years. Seventy-six percent of tumors (n=45) were parameningeal and 45% (n=26) were >5 cm. Of 45 M0 HNRMS patients treated with curative intent, 33 (73%) were E/A-HNRMS and 12 (27%) P-HNRMS. E/A-HNRMS patients received definitive RT with 66-70 Gy in 2 Gy per fraction. Elective nodal RT was routinely delivered. In the pre-IMRT era (before 2005), 12/23 (52%) patients with M0 E/A-HNRMS experienced loco-regional recurrences. In the IMRT era (2005 and onward), 1/10 (10%) patients with M0 disease recurred locally; this patient achieved a complete clinical response despite a 3-

week interruption after 48 Gy due to local toxicity, but experienced an in-field local recurrence 45 months later that resulted in death. Locoregional control was superior in the IMRT era vs pre-IMRT (p=0.049). Distant metastasis among patients with E/A-HNRMS was the predominant mode of treatment failure (n=17/33, 52%).

Conclusion:

Our study shows a high rate of locoregional control for adult E/A-HNRMS following definitive CRT using IMRT, and CRT should be considered for the majority of patients in this population. In contrast, P-HNRMS is distinct and requires surgery +/- RT.

Introduction

Rhabdomyosarcomas (RMSs) are a family of rare soft tissue sarcomas (STSs) that can present throughout the body. RMS are common childhood malignancies, constituting half of all soft-tissue sarcomas (STS), whereas adult RMS are exceedingly rare[1]. Soft tissue sarcomas make up 1% of adult malignancies, and RMS accounts for 3% of all soft tissue sarcomas[2]. Among adult RMS, 19% present with primary disease in the head and neck (HNRMS)[3].

The distribution of RMS histologic subtypes differs between pediatric and adult populations, with the embryonal histology being more common in children, pleomorphic more common in adults, and alveolar and spindle cell commonly found in both children and adults[3]. Given the rarity of the disease overall, no standard treatment for adult HNRMS exists[4], though management usually consists of a combination of radiation, chemotherapy, and surgery. [2] With regard to radiotherapy, technological advancements, particularly, intensity modulated radiotherapy (IMRT), have made delivery of high dose radiation to the head and neck area feasible by allowing high dose to targets while respecting normal tissue tolerance[5]. Chemotherapeutic management has also been refined with increased use of long course and maintenance regimens[6,7].

At our institution, a large tertiary cancer center, HNRMS have largely been treated with a uniform philosophy as part of a multidisciplinary sarcoma clinic. We report our experience with the presentation, management, and subsequent outcomes of adult patients with HNRMS

treated between 1984 – 2017, to contribute to the development of optimal management strategies for this rare family of diseases.

Methods

Our cohort includes adult (>16 years old) patients with HNRMS treated at XXXX in XXXX between 1984 to 2017 and was limited to patients registered in the multidisciplinary Sarcoma Clinic who received the majority of their treatment at our institution within the XXXX and XXXX in XXXX. A list of head and neck sarcoma patients were prospectively assembled from 1989 onwards. Additionally, from 2003 onward, HNRMS were prospectively registered in an in-house prospective Anthology of Outcome system where baseline characteristics, staging, treatment, and outcomes were collected at point-of-care[8]. Clinical information was supplemented by chart review for this study. The chart review process consisted of data obtained from the Electronic Patient Record (EPR), radiation therapy registration records (MOSAIQ), and hospital paper charts. A secondary review of histopathology was not performed, although all cases underwent prospective central pathology review by the XXXX pathology team as part of the multidisciplinary sarcoma team at the time each patient was registered and treated. Given the importance of known histological subtypes, which have been refined over recent decades with molecular studies for precise subtype determination, we therefore divided cases into two main categories: embryonal/alveolar (E/A-HNRMS) and pleomorphic (P-HNRMS). For uniform categorization, we retrospectively restaged patients using the AJCC TNM staging (8th edition) for soft-tissue sarcomas[9].

Treatment decisions were based on the recommendations of a multidisciplinary clinic. A consistent general philosophy of care was followed through these years. Localized pleomorphic RMS was predominantly treated with surgery +/- radiation, and occasionally with chemotherapy. Localized embryonal/alveolar RMS was predominantly treated with chemotherapy and radical radiation. Radiotherapy was delivered using 2-dimensional and 3-dimensional planning from 1980 through the early 2000's and IMRT from 2005 onward. Patients were followed post-treatment at 3-4 monthly intervals for the first two years, generally 4-6 monthly in the subsequent year, and generally annually thereafter according to feasibility. Follow-up information from the medical record was occasionally supplemented by communication with the family or referring physicians, as well as the cancer registry for vital status.

Summary statistics were generated for patient, disease, and treatment characteristics. Time to locoregional recurrence or systemic relapse was calculated from the first day of treatment. Statistical analyses were performed using the STATView 5.01. The Kaplan-Meier method was used to calculate survival rates. Prognostic variables including age, anatomic location, histologic subtype, radiation, and TNM classification were analyzed in univariate (UVA) Cox analyses using the log-rank statistic. Fisher's exact test was used to determine significant differences in locoregional control of embryonal/alveolar RMS between the pre-IMRT era (before 2005) and IMRT era (after 2005).

Results

Patient and disease characteristics

A total of 58 adult patients (>16 years of age) who met the inclusion criteria for the study were identified, with a median age of 32 years (range 16 to 81). Demographic and disease characteristics are presented in **Table 1**. The highest distribution was within the 16-30-year group and diminished with increasing age (**Figure 1**). The male: female ratio was 1:1.2. Seventy-six percent of tumors (n=45) were parameningeal and 45% (n=26) were >5 cm. Half of the patients (50%, n=29) had clinical node positive disease and 15% (n=9) had distant metastatic disease (M1) at the time of diagnosis. More than half of patients presented with a primary tumor originating within the paranasal sinuses (PNS). The median primary tumor size was 5 cm and the majority invaded contiguous tissues. Forty-five patients (78%) were diagnosed with embryonal/alveolar RMS and 13 patients (22%) with pleomorphic/undifferentiated RMS. Pleomorphic RMS was predominant in older patients (age range 67-82) and the majority did not present in the nasopharynx or PNS.

Median follow up for the whole cohort was 18 months (range: 5 – 226); median follow up for the pre-IMRT and IMRT eras were 20 months (range: 8 – 226) and 16 months (range: 5 – 98), respectively. A total of 5 patients were lost to follow up, 4 in the pre-IMRT era (after 28, 31, 125, and 226 months) and 1 in the IMRT era (after 17 months).

Patients typically had a short history of symptoms before presenting to a specialist physician. The median duration of symptoms prior to presentation to a tertiary care referral hospital was

9 weeks. Common presenting symptoms were nasal obstruction, facial pain or numbness, neck mass, proptosis, diplopia, epistaxis, and decreased visual acuity.

Treatment and patterns of recurrence for patients with initial M0 disease

Forty-five patients with M0 disease were treated with radical curative intent. Thirty-three (73%) had embryonal/alveolar RMS and 12 (27%) had pleomorphic RMS. In general, embryonal and alveolar RMS were treated sequentially with chemotherapy, concurrent chemoradiotherapy, and further chemotherapy. Pleomorphic RMS was generally treated similarly to other STS with surgery +/- radiation; three patients with non-metastatic pleomorphic RMS treated with curative intent received chemotherapy.

Only 2 patients with embryonal/alveolar RMS received surgical management, one for primary disease in the masticator space and the other in the soft palate. Surgery in both cases consisted of a diagnostic procedure to obtain tissue and both patients received adjuvant radiation. All other patients received radical primary radiation with either 66 Gy or 70 Gy in 2 Gy per fraction over 6.5-7 weeks. Involved nodal regions were always treated with radical dose RT, and elective nodal RT was standard practice. In the IMRT era, gross disease (GTV) was contoured based on imaging findings with CT and or MRI along with physical examination including flexible nasopharyngoscopy when indicated. RT regimens were typically 33 – 35 fractions. Clinical tumor volume (CTV) for the primary was created by expanding the GTV by approximately 5 mm and following routes of microscopic spread to create the high dose CTV (66 or 70 Gy); a lower dose level CTV of 56 Gy was created by expanding the GTV by 1 cm and following routes of

spread, which would also usually include adjacent paranasal sinuses. Nodal high dose CTVs similarly expanded the nodal GTV by 3 – 5 mm. Elective nodal regions were typically treated with 56 Gy and depended on the location of the primary tumor and involved nodal regions. The usual presentation of E/A-HNRMS was parameningeal and had extensive adenopathy, with elective nodal regions including retropharyngeal nodes, and levels 1-5. Due to the expected response of these tumors to chemotherapy received prior to RT, care was taken to cover the initial extent of disease to 56 – 63 Gy at the discretion of the treating physician. In the pre-IMRT era (i.e., before 2005), out of the 19 patients with primary disease in the nasopharynx or paranasal sinuses, 11 (58%) were treated with bilateral neck RT; the remainder of patients with well-lateralized disease were treated with ipsilateral neck RT, even with a clinically node negative neck. In the IMRT-era (from 2005 onwards), all 9 patients with primary disease in the nasopharynx or paranasal sinuses were treated with bilateral neck RT, while patients with well lateralized primary disease, such as in the parotid and orbit, were treated with ipsilateral neck RT. The average total chemotherapy duration was 183.5 weeks. Common regimens included VAC (vincristine, dactinomycin, and cyclophosphamide) or VAC with doxorubicin alternating with IE (ifosfamide and etoposide). Other regimens were used; VP-16, cisplatin, vinorelbine, and vinblastine were used less commonly.

The most common type of recurrence for patients with embryonal/alveolar RMS was distant metastases. Out of the 33 patients with initial M0 embryonal/alveolar RMS, 17 (52%) had distant metastasis to leptomeninges, testes, breast, heart, pericardium, pleura, peritoneum,

chest wall, subcutaneous tissue, lung, bone, and bone marrow. There was no statistical difference in rates of distant metastasis between the pre-IMRT and IMRT eras.

In the pre-IMRT era, out of the 33 patients with initial M0 embryonal/alveolar RMS, 12 (36%) had a loco-regional recurrence. In contrast, in the IMRT era, only one patient out of ten had a local recurrence; this patient achieved a complete clinical response despite a 3-week interruption after 48 Gy due to local toxicity (extensive grade 3 mucositis and tongue edema with emergent upper airway obstruction requiring inpatient admission). The patient experienced an in-field local recurrence 45 months later that resulted in death. In the IMRT era, no patients had a regional recurrence. The difference in locoregional recurrence comparing pre-IMRT to IMRT was statically significant (Fisher's exact test, p=0.049).

Among 12 patients with pleomorphic RMS, regional recurrence occurred in 1 who was initially clinically node positive. The patient was treated with surgery and adjuvant RT and also developed a local recurrence. Distant recurrence occurred in 4 (33%) patients, 2 of whom also had local recurrences. In total, 4 (33%) patients had a local recurrence, one of which was an isolated recurrence. Details of patients' disease, treatment, and patterns of recurrence can be found in **Table 2**.

Survival and prognostic factors

With a median follow-up of 18 months, among all adult HNRMS patients, 5-year overall survival (OS) was 34% (95% CI: 20%-48%) and 29% (95% CI: 17%-42%) for patients without and with distant metastatic disease at presentation, respectively. On univariable analysis, among patients with initial M0 disease, the following variables were associated with a worse OS: paranasal sinus involvement (HR 0.46, 95% CI 0.217-.987, p=0.046), increased tumor size (HR 1.028, 95% CI 1.007-1.049, p=0.0089), and decreased performance status (HR 2.133, 95% CI 1.291-3.523, p=0.0031).

Discussion

Given the rarity of adult HNRMS, standard-of-care management algorithms are difficult to establish, but all patients should benefit from assessment in a multidisciplinary setting with expertise in both head and neck cancer and sarcoma management, whenever possible[4]. Extrapolating from the pediatric literature, prolonged maintenance chemotherapy is now regarded as a critical aspect of management for embryonal and alveolar RMS to improve OS[6,7]. Our data supports this principle in that distant metastasis was the most common type of recurrence among these patients.

Among adult patients especially, there is a lack of consensus regarding optimal locoregional disease management of embryonal and alveolar HNRMS. For example, Hawkins et al advocated for surgical resection to negative margins whenever possible, and did not distinguish between embryonal/alveolar and pleomorphic in this recommendation[10]. Surgical management of

sarcoma in the head and neck may require disfiguring surgery that affects function. Furthermore, embryonal and alveolar HNRMS is characterized by high rates of distant metastatic recurrence and an excellent response to RT. For these reasons, our center has consistently treated adult embryonal/alveolar HNRMS with radical RT. In addition, potential late effects of RT, such as the risk of IQ/cognitive effects and growth effects are less likely in adults compared to children[11,12] and hearing, and endocrinopathies may also be less relevant. Furthermore, modern RT techniques such as IMRT and VMAT allow increased doses to target structures while respecting normal tissue tolerances, such as dose to the optic nerves and chiasm[13,14].

We observed no locoregional recurrences in the IMRT era among patients able to complete their course of RT. A single local recurrence occurred in a patient who required a three-week break after 48 Gy due to acute toxicity. This case was illustrative in several ways: the patient had a complete clinical and radiographic response after 48 Gy highlighting the radioresponsive nature of embryonal/alveolar RMS; the recurrence was in-field and happened after 45 months, highlighting the need for radical doses to obtain a durable response; and the severe toxicity requiring the treatment break highlights the toxic nature of concurrent chemotherapy and radiation regimen and the need for multidisciplinary support in a center with expertise managing these side effects of treatment. All of our embryonal/alveolar RMS patients treated with radical intent were treated to 66-70 Gy in 2 Gy per fraction, doses similar to head and neck RT for adult squamous cell carcinoma. Pre-IMRT, more locoregional recurrences occurred, and this difference was statistically significant. We hypothesize that this reflects that with 2D and

3D RT planning, proper target coverage while respecting normal tissue tolerances is often challenging[15,16]. With inadequate target coverage, risks for locoregional and marginal recurrences increase (**Figure 2**). It is well known that IMRT is highly beneficial for treatment of nasopharyngeal carcinoma, a clinical scenario with similar anatomic considerations to embryonal/alveolar adult HNRMS, which also often arises in the paranasal sinuses and nasopharynx. Peng et al demonstrated improved OS for nasopharyngeal carcinoma with IMRT as compared to conventional RT in a randomized trial[17]. We similarly observed that with modern RT techniques and planning, where radical doses are delivered to targets as intended, excellent locoregional control can be achieved for adult embryonal/alveolar HNRMS and surgical resection can be avoided.

Elective neck RT is a controversial management strategy for many HN malignancies. Due to our small sample size, our data do not clarify the role for RT in reducing regional recurrences in initially uninvolved necks. Ludmir et al reported on a series of patient with A-HNRMS in which elective nodal RT was not delivered, and found isolated nodal recurrence, with no nodal disease at diagnosis, in 75% of patients[18]. Within our institution, paranasal sinus, nasopharynx, and midline primary disease is more commonly treated with bilateral neck RT, with excellent locoregional control. Similarly, well lateralized primary disease is often treated with ipsilateral nodal RT, also with good results. In adults, where late effects relating to development and growth are not as critical compared to pediatrics, elective nodal RT is reasonable, especially in regions difficult to salvage and when the risk of occult nodal involvement is felt to be high and may be associated with ongoing risk of distant metastasis. In contrast to embryonal/alveolar

RMS, in our cohort, pleomorphic RMS was primarily treated with surgery +/- RT, and less frequently with elective nodal RT. This is in keeping with the philosophy that pleomorphic RMS behaves more like other soft tissue sarcoma with a lower risk of nodal involvement compared to embryonal/alveolar RMS.

Overall survival in our study was similar to other reported series, with 5-year OS among initially M0 patients of 34% (**Table 3**)[2,19–25]. These studies either did not report specifics of treatment, or reported highly variable treatment patterns over many years. This highlights the importance of results for this disease with a consistent treatment approach. Distant metastatic recurrence was the most common recurrence type, highlighting the importance of chemotherapy for this disease entity. Chemotherapy selection in the adult population is often extrapolated from the pediatric literature and cooperative group protocols[26]. Maintenance chemotherapy for high-risk embryonal RMS in the pediatric setting has been shown to improve OS and similar approaches in the adult population should be consdidered[6].

Given the many complexities in the diagnosis, workup, and treatment of RMS, it is crucial that patients with RMS are assessed in centers with expertise along the whole sarcoma cancer pathway from pathology with molecular testing, imaging, and multidisciplinary treatment decision making. In addition, for adults with head and neck RMS, expertise in head and neck cancer is also beneficial for surgery and radiotherapy considerations, as well as support of patients through treatment due to the anatomic complexities that may impact on psychosocial

as well as other functional problems addressing ocular, salivary, endocrine, speech and swallowing function, in addition to the challenge of disease eradication in these locations.

Our study is limited by the retrospective nature of a rare disease with population assembly over several decades. Although patients were treated with a consistent guiding philosophy throughout, a multitude of clinical decisions not captured in the electronic health record introduce selection bias. Given the rarity of this particular situation, despite having a relatively large sample of adult patients with head and neck RMS, the dataset is objectively small limiting the ability for multivariable modeling. Our study also spans over 3 decades during which treatment techniques and technology changed. Given the small sample size, time span of the analysis over several decades, and confounding related to the retrospective review and unknown variables, the results of the analysis of improved loco-regional recurrence in the IMRT era, while promising and in keeping with expected benefits of IMRT, cannot definitely be attributed to IMRT due to these limitations. Lastly, subsequent pathology review was not undertaken at the time of analysis, although remains a prospective centerpiece of the initial management and governed the management decisions undertaken by the treatment team at the time the patients were accrued. Therefore, we grouped diagnoses into embryonal/alveolar versus pleomorphic RMS which remains the standard classification of this disease, although we appreciate that modern molecular testing could identify evolution in the diagnoses, especially between the embryonal and alveolar subtypes, although we do not have evidence of this. Moreover, the embryonal/alveolar subtype (almost 80% of the study) demonstrated the expected disease behavior and response evident in the literature for these diseases.

Conclusion

Adult head and neck RMS are a rare and aggressive family of malignancies, with high rates of distant recurrence and death. Adult Embryonal/alveolar head and neck RMS can be controlled locoregionally with concurrent chemoradiotherapy using IMRT, and should be considered for management in this population, especially when the surgical resection needed would be extensive, such as craniofacial resection and orbital exenteration, which would be required for many of these patients but has functional and cosmetic consequences; it could also interrupt ongoing maintenance chemotherapy which has proven survival benefit and is a crucial component of the multimodal approach for these patients. Pleomorphic RMS are generally more suitably managed with an approach similar to other soft tissue sarcomas with surgery +/- RT and occasional chemotherapy. Further research is needed to better understand and care for this unique patient population.

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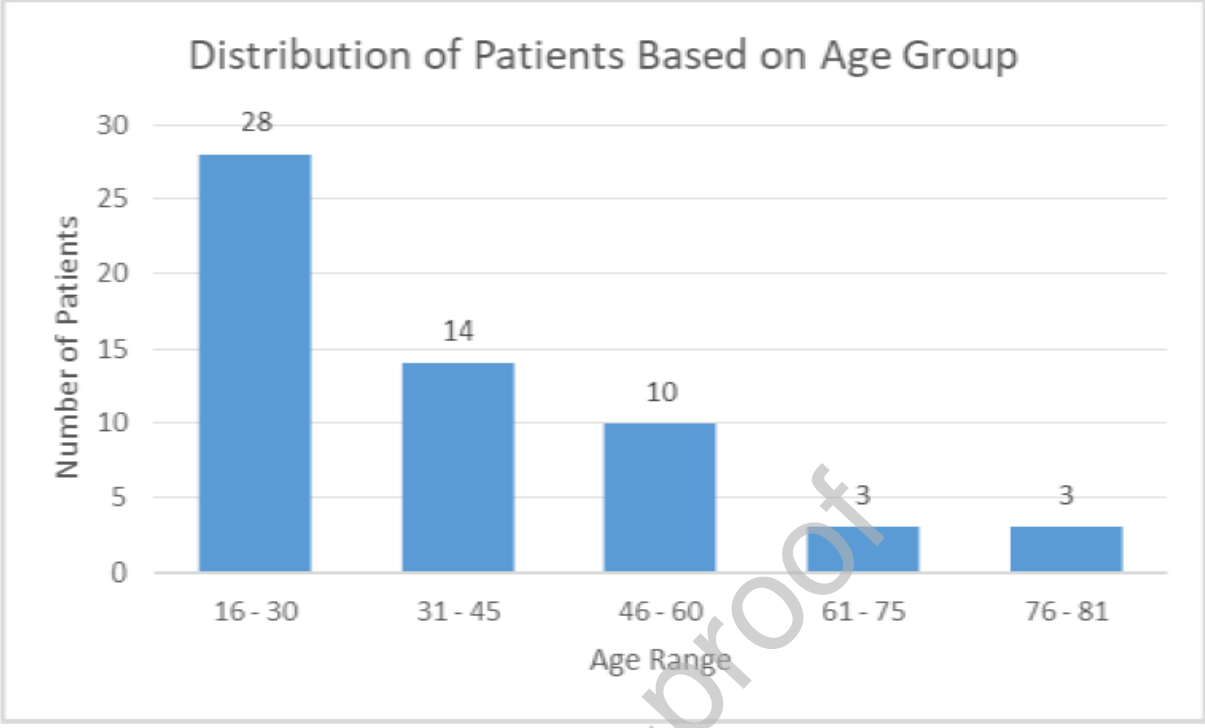

Figure 1. Distribution of Patients by Age.

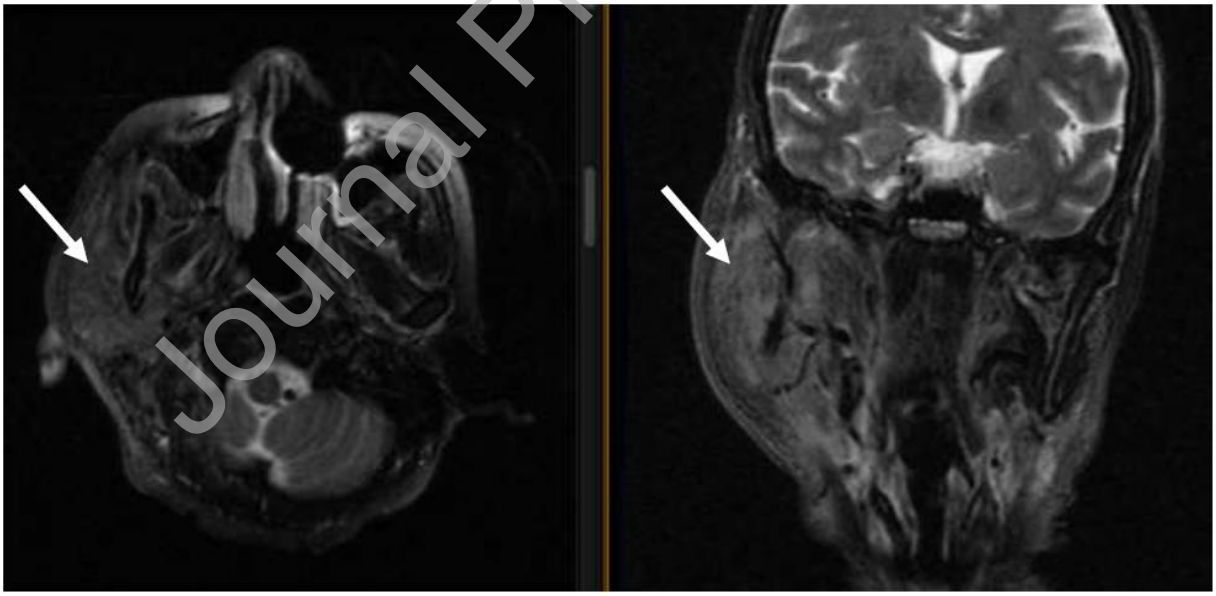

Figure 2. Fifty-six-year-old woman with paranasal sinus embryonal/alveolar rhabdomyosarcoma with bilateral neck adenopathy. She was treated in 2002 in the pre-IMRT era with a wax mold on the face incorporating a left eye shield allowing treatment with an

anterior field and two lateral wedge fields, and bilateral neck radiation. She achieved a complete radiographic response. The image below shows a marginal recurrence at the superior aspect of the neck volume and parotid on the right with no evidence of disease at the primary site or treated neck inferiorly; axial and coronal images of this marginal recurrence are depicted here (white arrows). She received palliative radiation to this recurrence, 30 Gy in 10 fractions. She developed osteoradionecrosis of the mandible from radiotherapy and myelodysplastic syndrome related to her chemotherapy. This case highlights the importance of IMRT for both target coverage, as well as normal tissue sparing.

Table 1. Patient Demographics and disease characteristics.

Variables	Frequency Number (%)
Age	
Median (range)	32 (16-81)
Sex	
Male	26 (45%)
Female	32 (55%)
ECOG Performance Status	
0-1	49 (85%)
≥ 2	9 (15%)
Symptom duration	
Median (weeks)	9
Primary Site	
Paranasal sinus	35 (60%)
Nasopharynx	7 (12%)
Oral cavity and oropharynx	5 (9%)
Larynx	2 (3%)
Parotids	2 (3%)
Orbit	2 (3%)
Masticator space	1 (2%)
Buccal space	1 (2%)
Infratemporal fossa	1 (2%)
Supraclavicular	2 (3%)
Parameningeal	45 (76%)
Primary size (cm)	
Median (range)	5 (1.5 – 16.6)
Primary tumor size	
≤ 5 cm	32 (55%)
> 5 cm	26 (45%)
Nodal involvement	
N0	29 (50%)
N1	29 (50%)
Histological subtype	
Embryonal	23 (40%)
Alveolar	22 (38%)
Pleomorphic/Undifferentiated	13 (22%)

Table 2. Breakdown of patients' histological diagnoses, anatomical subsites, treatment modalities, and patterns of recurrence.

Pre-2005 (pre-IMRT era)							
		Management			Recurrence		
	Number	Surgery	RT	Chemo	Local	Regional	Distant
Embryonal/Alveolar							
Ethmoid	11, N+ (5)	0	11	11	2	2	6
Maxillary	6, N+ (3)	0	6	6	3	2	4
Oral cavity	2, N0	0	1	2	1	1	1
Parotid	1, N0	0	1	1	0	0	0
Nasopharynx	2, N+ (1)	0	2	2	0	1	1
Orbit	1, N0	0	1	1	0	0	0
Pleomorphic/undifferentiated							
Larynx	1, N0	0	1	0	1	0	0
Neck	1, N0	1	1	0	1	0	1
Parotid	1, N0	1	1	0	0	0	0
Ethmoid	1, N0	0	1	1	0	0	0
Nasopharynx	1, N0	0	1	1	0	0	1
Post-2005 (IMRT era)							
		Management			Recurrence		
	Number	Surgery	RT	Chemo	Local	Regional	Distant
Embryonal/Alveolar							
Ethmoid	7, N+ (7)	0	7	7	0	0	3
Maxillary	1, N+	0	1	1	1	0	1
Soft palate	1, N0	1	1	1	0	0	0
Masticator space	1, N0	1	1	1	0	0	1
Pleomorphic/undifferentiated							
Larynx	1, N+	0	1	0	1	0	1
Neck	1, N0	1	0	1	0	0	0
Maxillary bone	1, N+	1	1	0	1	1	0
Soft palate	1, N0	1	0	0	0	0	0
Ethmoid	1, N0	1	1	1	0	0	1
Nasopharynx	2, N0	2	2	0	0	0	0

Table 3. Reported survival rates of adults with head and neck rhabdomyosarcoma.

Author (date)	Overall survival	Comments
Nakhleh (1991)[19]	20% (5-year crude)	12 adults
Nayar (1993)[20]	7.6% (5-yr)	26 adults
Callender (1995)[21]	32% (5-yr)	37 adults and children. Survival quoted is for patients >23 years (n=18).
Simon (2002)[22]	35.7% (5-yr)	49 adults and children. Survival quoted is for the patients >11yrs (n=24).
Little (2002)[23]	35% (10-yr)	82 adults with RMS (total, for all sites). Survival quoted is for 43 patients HNRMS
Ferrari (2003)[2]	46.7% (5-yr)	171 adults with RMS (total, for all sites). Survival quoted is for 48 patients with HNRMS
Esnaola (2001)[24]	31% (5-yr)	39 adults with RMS (all sites).
Wu (2014)[25]	36% (5-yr)	59 adults
Current study	34% (5-yr)	58 adults. Survival quoted is for 49 non-metastatic patients.