Scientific Article

Adult Head and Neck Rhabdomyosarcoma: Management, Outcomes, and the Effect of Intensity Modulated Radiation Therapy on Locoregional Control

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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 in which prognosis is better but treatment imperatives differ. We report management and outcomes of adult HNRMS treated over 3 decades.

Methods and Materials: Adult HNRMS treated from 1984 to 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. Intensity modulated radiation therapy (IMRT) was adopted from 2005 onward.

Results: Fifty-eight patients were eligible; the median age was 32 years. Seventy-six percent of tumors (n = 45) were parameningeal and 45% (n = 26) were >5 cm. Of 45 patients with M0 HNRMS treated with curative intent, 33 (73%) were E/A-HNRMS and 12 (27%) P-HNRMS. Patients with E/A-HNRMS received definitive RT with 66 to 70 Gy in 2 Gy per fraction. Elective nodal RT was routinely delivered. In the pre-IMRT era (before 2005), 12 of 23 (52%) patients with M0 E/A-HNRMS experienced locoregional recurrences. In the IMRT era (2005 and onward), 1 of 10 patients (10%) with M0 disease recurred locally; this patient achieved a complete clinical response despite a 3-week interruption after 48 Gy because of local toxicity but experienced an in-field local recurrence 45 months later.

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that resulted in death. Locoregional control was superior in the IMRT era vs pre-IMRT era ($P = .049$). Distant metastasis among patients with E/A-HNRMS was the predominant mode of treatment failure ($n = 17$ of $33$, $52\%$).

**Conclusions:** 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.

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### Introduction

Rhabdomyosarcomas (RMS) are a family of rare soft tissue sarcomas (STS) that can present throughout the body. RMS are common childhood malignancies, constituting half of all STS, whereas adult RMS are exceedingly rare. STS make up $1\%$ of adult malignancies, and RMS account for $3\%$ of all STS. Among adult RMS, $9\%$ present with primary disease in the head and neck (HNRMS).

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. Given the rarity of the disease overall, no standard treatment for adult HNRMS exists, though management usually consists of a combination of radiation, chemotherapy, and surgery. With regard to radiation therapy, technological advancements, particularly intensity modulated radiation therapy (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. Chemotherapeutic management has also been refined with increased use of long course and maintenance regimens.

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 and 2017 to contribute to the development of optimal management strategies for this rare family of diseases.

### Methods and Materials

Our cohort includes adult ($>16$ years of age) patients with HNRMS treated at Princess Margaret Cancer Centre in Toronto, Canada 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 University Health Network and Mount Sinai Hospitals in Toronto. A list of patients with HNRMS 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. Clinical information was supplemented by chart review for this study. The chart review process consisted of data obtained from the Electronic Patient Record, 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 University Health Network or Mount Sinai Hospital pathology team as part of the multidisciplinary sarcoma team at the time each patient was registered and treated. Given the importance of known histologic subtypes, which have been refined over recent decades with molecular studies for precise subtype determination, we therefore divided cases into 2 main categories: embryonal/alveolar (E/A-HNRMS) and pleomorphic (P-HNRMS). For uniform categorization, we retrospectively restaged patients using the American Joint Committee on Cancer tumor, node, metastases staging (eighth edition) for STS.

Treatment decisions were based on the recommendations of a multidisciplinary clinic. A consistent general philosophy of care was followed through these years. Localized P-RMS was predominantly treated with surgery +/- radiation and occasionally with chemotherapy. Localized E/A-RMS was predominantly treated with chemotherapy and radical radiation. Radiation therapy was delivered using 2- and 3-dimensional planning from 1980 through the early 2000s and IMRT from 2005 onward. Patients were followed posttreatment at 3- to 4-month intervals for the first 2 years, generally at 4- to 6-month intervals 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 STATView 5.01 (SAS Institute Inc.). The Kaplan-Meier method was used to calculate survival rates. Prognostic variables including age, anatomic location, histologic subtype, radiation, and tumor, node, metastases classification were analyzed in univariate Cox analyses using the log-rank statistic. A Fisher exact test was used to determine significant differences in locoregional control of E/A-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, 16-81). Demographic and disease characteristics are presented in Table 1. The highest distribution was within the 16- to 30-year group and diminished with increasing age (Fig. 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 at the time of diagnosis. More than half of patients presented with a primary tumor originating within the paranasal sinuses. The median primary tumor size was 5 cm, and the majority invaded contiguous tissues. Forty-five patients (78%) received diagnoses of E/A-RMS and 13 patients (22%) of pleomorphic/undifferentiated RMS. P-RMS was predominant in older patients (range, 67-82 years) and the majority did not present in the nasopharynx or paranasal sinuses.

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 before 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 E/A-RMS and 12 (27%) had P-RMS. In general, patients with E/A-RMS were treated sequentially with chemotherapy, concurrent chemoradiotherapy, and further chemotherapy. Patients with P-RMS were generally treated similarly to other STS with surgery +/- radiation; 3 patients with M0 P-RMS treated with curative intent received chemotherapy.

Only 2 patients with E/A-RMS received surgical management: 1 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 to 7 weeks. Involved nodal regions were always treated with radical dose RT, and elective nodal RT was standard practice. In the IMRT era, gross tumor volume (GTV) was contoured based on imaging findings with computed tomography and/or magnetic resonance imaging along with physical examination including flexible nasopharyngoscopy when indicated. RT regimens were typically 33 to 35 fractions. Clinical tumor volume (CTV) for the primary was

| Variable                        | Frequency         |
|---------------------------------|-------------------|
| Age, median (range)             | 32 (16-81)        |
| Sex, n (%)                      |                   |
| Male                            | 26 (45)           |
| Female                          | 32 (55)           |
| ECOG performance status, n (%)  |                   |
| 0-1                             | 49 (85)           |
| ≥2                              | 9 (15)            |
| Symptom duration (wk), median   | 9                 |
| Primary site, n (%)             |                   |
| 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, n (%)            | 45 (76)           |
| Primary size (cm), median (range)| 5 (1.5-16.6)      |
| Primary tumor size, n (%)       |                   |
| ≤5 cm                           | 32 (55)           |
| >5 cm                           | 26 (45)           |
| Nodal involvement, n (%)        |                   |
| N0                              | 29 (50)           |
| N1                              | 29 (50)           |
| Histologic subtype, n (%)       |                   |
| Embryonal                       | 23 (40)           |
| Alveolar                        | 22 (38)           |
| Pleomorphic/Undifferentiated    | 13 (22)           |

Abbreviations: ECOG = Eastern Cooperative Oncology Group.
typically created by expanding the GTV by approximately
5 mm and following routes of microscopic spread to cre-
ate 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. For disease
involving parameningeal sites, care must be taken with
intracranial margins due to the risk of local recurrence
and leptomeningeal relapse, balancing gains in local con-
control with toxicities of treatment. Nodal high dose CTVs
similarly expanded the nodal GTV by 3 to 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 adenop-
athy, with elective nodal regions including retropharyng-
eal nodes and levels 1 to 5. Due to the expected response
of these tumors to chemotherapy received before RT, care
is taken to cover the initial extent of disease to 56 to 63
Gy at the discretion of the treating physician. In the pre-
IMRT era (ie, before 2005), out of the 19 patients with pri-
mary 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 vincristine, daclino-
mycin, and cyclophosphamide with or without doxorubi-
cin alternating with 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
E/A-RMS was distant metastases. Out of the 33 patients
with initial M0 E/A-RMS, 12 (36%) had a locoregional recurrence. In
contrast, in the IMRT era, only 1 patient out of 10 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 exact
test, \( P = .049 \)).

Among 12 patients with P-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 patients (33%), 2 of whom also had local
recurrences. In total, 4 patients (33%) had a local recur-
rence, 1 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 patients with HNRMS, 5-year overall survival (OS)
was 34% (95% confidence interval [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 dis-
ease, the following variables were associated with a worse
OS: paranasal sinus involvement (hazard ratio [HR], 0.46;
95% CI, 0.217-0.987; \( P = .046 \)); increased tumor size (HR,
1.028; 95% CI, 1.007-1.049; \( P = .0089 \)); decreased per-
formance status (HR, 2.133; 95% CI, 1.291-3.523;
\( P = .0031 \)).
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. 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. Our data supports this principle in that distant metastasis was the most common type of recurrence among these patients.

| Table 2 Breakdown of patients’ histologic diagnoses, anatomic subsites, treatment modalities, and patterns of recurrence |
|---------------------------------------------------------------|
| **Number Management Recurrence** |
| **Surgery** | **RT** | **Chemo** | **Local** | **Regional** | **Distant** |
| **Pre-2005 (pre-IMRT era)** |
| 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 | 0 | 1 | 0 | 1 | 0 | 1 |
| Parotid | 1, N0 | 0 | 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)** |
| 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 | 0 | 1 | 0 | 0 | 0 | 0 |
| Maxillary bone | 1, N+ | 1 | 1 | 1 | 1 | 0 | 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 |

Abbreviations: Chemo = chemotherapy; IMRT = intensity modulated radiation therapy; RT = radiation therapy. The numbers in parentheses are the number who are N+, node positive.

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. 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. 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 E/A-HNRMS. For example, Hawkins et al advocated surgical resection to negative margins whenever possible and did not distinguish between embryonal/alveolar and pleomorphic in this recommendation. Surgical management of sarcoma in the head and neck may require disfiguring surgery that affects function. Furthermore, E/A-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 E/A-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 with children, and hearing and endocrinopathies may also be less relevant. Furthermore, modern RT techniques such as IMRT and volumetric modulated arc therapy allow increased doses to target structures while respecting normal tissue tolerances, such as dose to the optic nerves and chiasm.

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 3-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 E/A-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 this 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 patients with E/A-RMS treated with radical intent were treated to 66 to 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 2- and 3-dimensional RT planning, proper target coverage while respecting normal tissue tolerances is often challenging. With inadequate target coverage, risks for locoregional and marginal recurrences increase.

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−intensity modulated radiation therapy era with a wax mold on the face incorporating a left-eye shield allowing treatment with an anterior field and 2 lateral wedge fields and bilateral neck radiation. She achieved a complete radiographic response. These images show 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 with white arrows. She received palliative radiation to this recurrence: 30 Gy in 10 fractions. She developed osteoradionecrosis of the mandible from radiation therapy and myelodysplastic syndrome related to her chemotherapy. This case highlights the importance of intensity modulated radiation therapy for both target coverage as well as normal tissue sparing.

Elective neck RT is a controversial management strategy for many head and neck 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 alveolar-HN RMS in which elective nodal RT was not delivered, and found isolated nodal recurrence, with no nodal disease at diagnosis, in 75% of patients. 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 with 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 E/A-RMS, in our cohort, P-RMS was primarily treated with surgery +/- RT, and less frequently with elective nodal RT. This is in keeping with the philosophy that P-RMS behaves more like other STS with a lower risk of nodal involvement compared with E/A-RMS.

Overall survival in our study was similar to other reported series, with 5-year OS among initially M0 patients of 34% (Table 3).2,18-24 These studies 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.25 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 considered.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 HNRMS, expertise in head and neck cancer is also beneficial for surgery and radiation therapy considerations, as well as support of patients through treatment. Specialized support is frequently needed 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 HNRMS, the data set 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. Last, 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 E/A-RMS versus P-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 E/A subtypes. Moreover, the E/A subtype (almost 80% of the study) demonstrated the expected disease behavior and response evident in the literature for these diseases.

### Conclusion

Adult HNRMS are a rare and aggressive family of malignancies, with high rates of distant recurrence and death. Adult E/A-HNRMS 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. P-RMS are generally more suitable managed with an approach similar to other STS with surgery +/- RT and occasional chemotherapy. Further research is needed to better understand and care for this unique patient population.

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