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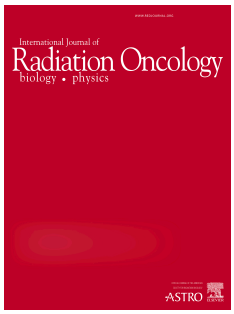

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Patterns of Failure in Parameningeal Alveolar Rhabdomyosarcoma

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Abstract

Purpose: To determine patterns of failure, clinical outcomes, and prognostic factors among pediatric patients treated with radiotherapy for parameningeal alveolar rhabdomyosarcoma (ARMS).

Methods: We evaluated clinical and treatment planning records of children aged ≤21 years with parameningeal ARMS treated with definitive or adjuvant radiotherapy at our institution. The Kaplan-Meier product limit method assessed disease control and survival; the log-rank test was used to evaluate prognostic impact.

Results: We identified 24 patients with a median age of 3.5 years (range, 1–20) treated between 2009 and 2016. The median follow-up was 2.4 years for all (range, 0.3–5.6) and 3.2 years for living patients (range, 0.7–5.6). Most patients had group III (96%), node-negative (67%), positive FOX fusion status (63%) disease and intracranial extension (54%). The paranasal sinus was the most common subsite (29%).

All patients were treated with concurrent chemotherapy and proton radiotherapy with a median dose of 50.4GyRBE (range, 41.4–59.4) at a median 13 weeks, following induction chemotherapy (range, 3–25). The 3-year local control, regional control, disease-free survival, and overall survival rates were 66%, 94%, 40%, and 58%, respectively. Median time to any failure was 0.5 years (range, 0.2–2.1). N1 disease and intracranial extension (ICE) portended inferior overall survival (p=0.002 and 0.02, respectively). Female sex portended better local control (p=0.05). All 7 patients with distant metastases as the first site of recurrence had central nervous system metastases. Age <4 years, absence of ICE, N0 disease, and primary tumor <5cm were associated with a statistically significant improvement in freedom from distant metastases.

Conclusion: While regional nodal failures were rare, in-field local recurrences and leptomeiningeal progression in those with ICE suggest the need for modification of local and central nervous system therapies.

Introduction

In patients with rhabdomyosarcoma, parameningeal location is considered an unfavorable factor by both the North American and European staging systems. Approximately half of parameningeal tumors present with regional nodal disease and over a quarter with distant metastases (1). These tumors are able to extend intracranially to the leptomeninges, resulting in neoplastic meningitis (2). The presence of intracranial extension (ICE), skull base erosion, and cranial nerve palsy may also portend a worse survival (3).

Reports of regional failures after radiotherapy (RT) for head and neck rhabdomyosarcoma have generated discussion of sentinel lymph node biopsy (SLNB) for staging or elective nodal irradiation (ENI) in high-risk subsets. Ambiguity surrounding this issue is understandable, as even contemporary reports of parameningeal RMS patients offer widely variable estimates of regional disease control (4, 5). Leptomeningeal failures also complicate patterns of failure analyses in parameningeal RMS, and these CNS relapses often have dire consequences (5-9). There is a clear need to better define patterns of failure so we can appropriately tailor treatment in this vulnerable population and this requires large but relatively homogeneous patient cohorts treated in a uniform manner. This study reports clinical outcomes and prognostic factors in pediatric patients with parameningeal alveolar rhabdomyosarcoma treated in the modern era.

Materials and Methods

Twenty-four consecutive children aged ≤ 21 years with non-metastatic parameningeal alveolar rhabdomyosarcoma were treated between 2009 and April 2018 under an institutional review board-approved prospective outcome study (IRB# 2006-153). All patients received either definitive or adjuvant radiation at our institution. Patients who had received prior radiation were excluded.

All patients received induction, concurrent, and adjuvant chemotherapy, the majority per contemporary Children's Oncology Group (COG) (14 cycles of chemotherapy, randomized between VAC [vincristine, actinomycin D, and cyclophosphamide] and VAC/VI [with vincristine and irinotecan] for ARST0531) (10) or European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) (25 weeks of IVA (ifosfamide, vincristine, actinomycin D) with or without vinorelbine and cyclophosphamide for 24 weeks, depending on risk level) regimens (11). In the St. Jude RMS 13 regimen, the chemotherapy regimen consisted of VAC for 14 cycles followed by maintenance chemotherapy from weeks 43-60 with oral cyclophosphamide, bevacizumab, and sorafenib (12). Proton therapy was delivered to all patients according to institutional guidelines, which generally reflect international cooperative group protocols. Target delineation was based on initial and postinduction magnetic resonance imaging (MRI) (and positron emission tomography [PET], if available) fused with the computed tomography (CT) simulation images. For the primary tumor, the gross tumor volume (GTV) was defined by the gross disease at the time of radiation. The initial clinical target volume (CTV1)-primary was defined by the GTV-primary + 5 mm, with further modification as necessary to encompass all tissue originally infiltrated by the tumor. CTV2-primary was identical to GTV-primary. For a node-negative neck, the lymphatics were not treated. For a neck with radiographic or biopsy-proven nodal involvement, the grossly abnormal node(s) was defined as GTV-LN and the involved lymph node level(s) was defined as CTV1-LN. CTV2-LN was equivalent to GTV-LN (with no CTV expansion). Each CTV (primary and node) was expanded 3 mm for the creation of the PTV. Prescription doses, delivered at 1.8 GyRBE fractions using sequential plans, are displayed in **Table 1**.

Treatment planning goals included a prescription dose covering >99% of the CTV and >95% of the PTV. Underdosing of the target volume was accepted if necessary to meet optic chiasm, brainstem, or spinal cord constraints. One patient was treated with pencil-beam scanning (PBS) for the initial phase and

double-scattering for the boost phase; otherwise, all patients were treated with double-scattered proton plans.

ICE was defined as radiographic evidence of tumor invasion into the cranium on the pretreatment diagnostic MRI. Nodal involvement was defined as a positive lymph node biopsy or unequivocal reading of abnormal lymph node(s) on the official MRI or PET imaging report. All cases were reviewed in a multidisciplinary pediatric skull base and neurooncology tumor board. The tumor at initial diagnosis was contoured at the time of treatment planning, as was the residual gross disease for all group III patients who did not undergo delayed primary excision (DPE). The volume of the tumor in cm^3 was obtained from these delineations. In-field recurrence was defined as >80% of the recurrence volume within the 95% isodose line of the prescription dose. Marginal failure was defined as >20% to <80% of the recurrence volume receiving ≥95% of the prescription dose. An out-of-field recurrence occurred when <20% of the volume received ≥95% of the prescribed dose.

Acute and late treatment toxicity information was collected and graded prospectively according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0, during weekly on-treatment and follow-up visits.

All statistical analyses were performed with SAS and JMP software (SAS Institute, Cary, NC). The Kaplan-Meier product limit method provided estimates of disease control calculated from the start of radiation. The log-rank test was used to evaluate the prognostic impact between strata of selected variables for each endpoint. Prognostic factors were carefully selected and limited based on prior published data on rhabdomyosarcoma and other childhood solid tumors. Radiation dose correlation was assessed with Fisher's exact test.

Results

The median age at the time of radiation was 3.5 years (range, 1–20.3 years). Twenty-three patients were classified as COG group III (96%) and 20 (83%) had stage 3 disease. The median tumor size was 5.5 cm (range, 1.8–9cm). Patient, disease, and treatment characteristics are shown in **Table 2**.

For staging, all patients had MRI of the primary site, chest CT, and bone marrow biopsy; 75% had lumbar puncture, all with a negative result; and 42% underwent PET at initial diagnosis. No patients had a PET after induction chemotherapy. Positive lymph nodes were identified in 8 patients (33%), 3 by biopsy and 5 by imaging only. Three patients had indeterminate lymph nodes on imaging, with subsequent biopsies that were negative. ICE was visible radiographically on MRI in 54% of patients. Two of these patients also had an abnormal neurologic physical exam with facial weakness at initial diagnosis.

Induction and concurrent chemotherapy were used for all patients (**Table 2**). The cyclophosphamide dose on ARST0531 was 1.2 g/m^2/course. In EpSSG protocols, ifosfamide is used instead of cyclophosphamide. One patient had cyclophosphamide substituted for ifosfamide for 2 cycles due to toxicity. Proton therapy was delivered at a median week 13 (range, 3–25 weeks). There was no difference in the timing of proton therapy for those with and without ICE (week 12 vs 14, p= 0.16). The median radiation dose was 50.4 GyRBE. One group III patient underwent DPE with an R1 resection and another had a complete radiographic response to induction chemotherapy, dictating a dose reduction to 41.4 GyRBE on protocol. One patient stopped treatment early (at 45 GyRBE rather than the planned 50.4 GyRBE) due to internal jugular vein thrombosis related to the central line with complications requiring intensive care. No patients received a photon component. Anesthesia (intravenous propofol and inhalational sevoflurane) was used for 17 patients, all under the age of 5 years.

The median follow-up was 2.4 years (range, 0.3–5.6 years) for all patients and 3.2 years (range, 0.7–5.6 years) for living patients. As shown in **Figure 1A**, the 3-year local control rate was 66% (95% CI 42-84%)

and the regional nodal control rate was 94% (95% CI 66-99%). The 3-year freedom from distant metastases rate was 70% (95% CI 49-85%). All distant metastases occurred within the leptomeningeal compartment. The overall and progression-free survival rates at 3 years were 58% (95% CI 37-75%) and 40% (95% CI 23-61%), respectively (**Figure 1B**).

The median time to any failure was 0.5 years (range, 0.2–2.1 years). All local failures occurred in-field. The single nodal failure developed in the submental nodal basin. Seven patients developed distant metastases as the first site of recurrence, 6 leptomeningeal and 1 brain parenchyma (**Figure 2**). Chemotherapy regimen did not correlate with local control, central nervous system (CNS) failure, or overall survival (p=0.81, p=0.89, and p=0.86, respectively). No patients developed distant metastases outside of the CNS. Of the patients with disease progression, all who developed CNS progression expired within 13 months of relapse. Of note, 6 of the 7 patients with CNS progression had node-positive disease at diagnosis. Two of the 6 patients with a local recurrence are still alive after management with chemotherapy alone and chemotherapy plus surgery (**Table 3**).

The 3-year local and regional control rates were 61% and 93% in node-negative patients compared to 100% and 100% in node-positive patients (p=0.29 and p=0.71, respectively). The 3-year rate of freedom from CNS failure was 45% in those with ICE at diagnosis compared to 100% in those without (p=0.01). On univariate analysis, only sex correlated with local control: 90% in females vs 42% in males (p=.047). Inferior overall survival was seen in patients with ICE present at diagnosis (at 3 years, 38% with vs. 81% without ICE, p=0.02) and nodal positivity (at 3 years, 19% N1 vs 75% N0, p=0.002). Age <4 years, absence of ICE, and primary tumor <5 cm each correlated with a statistically significant advantage in freedom from distant metastases (**Table 4**). There was no correlation between use of staging PET at diagnosis and nodal positivity (p=0.67). Radiographic response to induction chemotherapy did not correlate with local control (p=0.37), CNS failure (p=0.28), or overall survival (p=0.66). Fusion status was analyzed and no statistically significant differences were identified, although this analysis is limited by small numbers. Of

the patients who did not undergo staging lumbar puncture, 1 developed a leptomeningeal recurrence, 1 a local recurrence, and 1 a regional recurrence; the other 3 did not experience disease progression. Significant acute and late toxicity is reported in **Supplementary Table 1**. No grade 4 or 5 acute or late toxicity occurred.

Discussion

Parameningeal alveolar RMS presents one of the greatest challenges in the management of non-metastatic RMS. The extent of function-preserving surgical resection is often limited due to intertwined critical structures and, in some cases, intracranial extension. The potential for radiation-related morbidity from the treatment of parameningeal sites is also high, with possible negative effects on cognition, bone growth, hormone function, vision, hearing, dentition, and deglutition. Local failure is more common in tumors >5 cm (13, 14) and there are wide estimates of regional failure in the literature (5, 6, 15). The current COG study ARST1431 is assessing dose escalation to 59.4 Gy for tumors >5 cm in efforts to improve local control for large tumors (16). These factors relating to local failure and morbidity have led to discussion of the need for an altered treatment paradigm in the subset of children afflicted by parameningeal alveolar RMS.

Yang et al (6) reported on a heterogenous cohort of 47 patients with parameningeal RMS, including 21% over age 21, 26% with stage 4 disease, and 57% with embryonal histology, treated with IMRT to 50.4 Gy in 1.8-Gy fractions. In a subset of patients aged > 14 years with alveolar RMS (n=13), ENI was delivered to the bilateral uninvolved cervical nodal levels in 1.3 Gy fractions using a dose-painting technique. Of note, 10 of these had ≥1 involved cervical node. The overall 5-year freedom from regional recurrence in this study was similar to our results at 3 years (92% and 94%, respectively). However, for patients with alveolar disease, regional failure reached 26%, in contrast to our experience of no regional failures in

patients with N1 disease and 1 regional failure (6%) in those with N0 disease. In the Yang et al study, there were no regional failures in the N0 cohort who received ENI. In the younger patients with alveolar histology who did not receive ENI, the regional failure rate was 37%, also contrasting our results. However, the Yang study did have similar findings to those of Ludmir et al (5). In a study of 14 patients with alveolar head and neck RMS (57% parameningeal) treated with proton therapy, the crude regional failure rate was 57% for the entire cohort and 75% for those with N0 disease. ENI was not used. In the setting of N1 disease, the gross nodal disease with a CTV margin was treated to 50.4 GyRBE. The authors describe that "the complete nodal basin for the involved nodal sites was not targeted for treatment." In their series, 2 of 6 patients with N1 disease had a nodal failure in the initially involved nodal basin, an area that would have received ≥36 Gy with our treatment approach. Importantly, the authors state that their practice has since changed to include the involved nodal basin. Reassuringly, in patients with N1 disease our approach of 36 Gy to the involved nodal levels with 50.4 Gy to involved nodes resulted in no regional nodal failures.

The experience by Ludmir et al study also reported 6 isolated nodal failures in 8 patients with N0 disease (5). All nodal failures occurred in the first-echelon draining nodal basin on the ipsilateral side to the tumor. Our approach of treating just the primary tumor matched the approach used by Ludmir et al, yet with notably different rates of regional failure. The difference in type of chemotherapy is a possible explanation for this difference in nodal failures in the clinical node-negative neck, as almost 2/3 of our cohort received ifosfamide, rather than the reduced-dose cyclophosphamide. Furthermore, 42% (10/24) of our cohort had staging PET compared to 29% (4/14) in the Ludmir et al study; however, we did not find a correlation between use of staging PET and diagnosis of involved lymph nodes. Turpin et al reported on the use of SLNB in head and neck RMS and advocate for this approach for both parameningeal and non-parameningeal subsites and all histologies (17). In their cohort of 6 patients (3 alveolar, 2 embryonal, and 1 spindle cell), 2 had negative MRI and PET imaging and subsequent negative

SLNB, 2 had positive radiographic findings for nodal involvement and positive SLNB, and 2 had incongruent findings (1 with positive imaging and negative SLNB and 1 with negative imaging and positive SLNB). Interestingly, both patients with discordant imaging and pathology had alveolar histology. While no patients underwent SLNB in our series, 4 had imaging concerning for nodal disease with negative targeted nodal biopsy, 3 had suspicious imaging with positive targeted nodal biopsy, and 5 were diagnosed with node-positive disease by imaging alone. There is the possibility that radiographically occult lymph node micrometastases are adequately addressed with systemic chemotherapy alone.

The 3-year local control rate was 66% in our series. While this nominally appears lower than other intermediate-risk RMS cohorts (4-6, 13, 15, 18, 19), our series included only those with the most unfavorable features: only alveolar histology, only parameningeal location, >95% group III, and median tumor size >5 cm. Nonetheless, a 3-year overall survival rate of 58% was similar to other series with more favorable cohorts (5, 6, 15). Target volumes for rhabdomyosarcoma have gradually decreased over time in cooperative group and single-institution studies. Under the close oversight of our prospective outcome protocol, our approach has been similar to push forward aggressively with radiation toxicity reduction. This approach requires validation in a larger patient cohort, but, reassuringly, marginal misses were not seen in our series of conformal proton therapy with smaller target margins compared to earlier photon studies (13). Increased local failure rates in current and recent rhabdomyosarcoma studies have resulted in concern regarding the reduced cyclophosphamide dose (8, 20-22). In ARST0531, the overall local failure rate was 9% higher compared to D9803 (22). This decrease in local control could not be explained by the inclusion of infants on that study. All North American patients in our cohort received the lower cyclophosphamide dose, while the European patients were treated with ifosfamide. There was no correlation between chemotherapy regimen and disease control or overall survival in our cohort.

With our treatment paradigm, CNS failures were the dominant pattern of failure (n=7) rather than regional lymphatics (n=1). CNS failure was the only distant metastatic development in our cohort, but it developed at a concerning rate of 55% in those with ICE (compared to 0% in those without ICE). Yang et al reported a 30% CNS failure rate at 5 years in those with ICE (and likewise 0% in those without ICE) (6). In the cohort from Ludmir et al, 14% had leptomeningeal failure overall, but of those with ICE, the leptomeningeal failure rate was 100% (2/2) (5). Lucas et al reported 4 leptomeningeal recurrences in a series of 13 patients with parameningeal rhabdomyosarcoma enrolled on RMS13 (8). All 4 of these patients had cranial nerve palsy at diagnosis, which prompted a protocol amendment to start radiotherapy at week 3 rather than week 12 for parameningeal tumors with high-risk features. RMS13 also uses the lower dose of cyclophosphamide (1.2 g/m^2). De et al reported on 23 patients with CNS failures over a 17-year period (1999 to 2016) (7). Over half were parameningeal primaries, and 92% of these had ICE. The timing of radiotherapy has varied over past protocols. Spalding et al reported no difference in local control between patients with cranial nerve palsy or skull based erosion on D9803 (radiation started week 12) compared to IRS-IV (radiation started day 0), but patients with ICE were recommended to start radiation on day 0 in both protocols, prohibiting evaluation of the effect of radiation timing on outcomes in those with ICE (23). Ludmir et al found a statistically significant difference in progression-free survival in patients with ICE, with no disease progression in 4 patients who started radiotherapy earlier than week 4, compared to 6 of 7 patients with progression treated with radiotherapy beyond week 4 (p=0.006) (24). In our series, 6 of the 7 patients with CNS progression had node-positive disease at diagnosis. As there is no pathophysiologic reason patients with lymphatic involvement should have an increased risk of leptomeningeal spread, we interpret this relationship as an indicator of overall tumor aggressiveness and propensity to disseminate beyond the primary site. Participants in the aforementioned studies included those treated with both photon and proton therapy, suggesting that leptomeningeal failure is not unique to proton therapy. Modality was

specifically examined by Casey et al, who found no statistically significant difference in local control, event-free survival, or overall survival for patients treated with protons versus IMRT in a cohort of pediatric patients with head and neck rhabdomyosarcoma (22).

All together, these data suggest that leptomeningeal recurrences remain a major concern in alveolar RMS patients with ICE and cranial nerve palsy. Whether through radiotherapy dose escalation, a shorter window of induction therapy, or novel CNS directed therapy, future studies should consider innovative measures to address this risk. CNS failures are rarely, if ever, salvageable (7). Historically, treatment with whole-brain radiotherapy with or without spinal irradiation and/or intrathecal chemotherapy was used to protect against CNS failure (18, 25, 26). However, treatment paradigms shifted away from these interventions due to high toxicity and a lack of evidence supporting improved disease control with these approaches (27). Our data suggest that prevention of leptomeningeal failure could improve survival in patients with intracranial extension. The importance of adequate chemotherapy for local control cannot be underestimated, as has been demonstrated by the reduction in cyclophosphamide dose on recent clinical trials. Selective chemotherapy intensification such as drugs with high CNS penetrance for alveolar parameningeal RMS with ICE at diagnosis should be evaluated in clinical trials to prevent this deadly pattern of failure. Radiation therapy earlier in the treatment paradigm may also be impactful. If these treatment modifications are inadequate, the risk-benefit ratio of reverting to the earlier treatment paradigm of CNS-directed radiation and chemotherapy may need reconsideration for a select cohort at high risk of CNS failure. Future studies might also consider the utility of a second LP prior to local therapy in these high-risk patients. If CNS failures can be eliminated, continued close investigation of patterns of failure is warranted, as the local and regional control may be impacted.

Limitations of this study include the small sample size, given the rarity of the disease. The small sample size may limit the detection of possible differences within the cohort on univariate analysis and also precludes multivariate analysis.

Conclusion

In this series of pediatric patients treated with proton therapy and concurrent chemotherapy for alveolar paramengineal RMS, nodal failures were rare. In patients with N0 disease, the 3-year regional failure rate was 7% in the absence of elective nodal irradiation. In patients with N1 disease, 36 Gy to the involved nodal levels with 50.4 Gy to involved nodes resulted in no regional nodal failures. Following our treatment paradigm, CNS failures were the dominant pattern of failure (n=7). In-field local recurrences and leptomeningeal progression in those with ICE suggest the need for modification of both local and CNS therapies.

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Figure Legends

Figure 1. Kaplan-Meier curves for (A) local control (66%), regional control (94%), and freedom from distant metastases (70%) and (B) disease-free survival (40%) and overall survival (58%) at 3 years.

Figure 2. (A) A representative case of a maxillary sinus alveolar rhabdomyosarcoma with involvement of the orbit and nasal cavity at the time of initial diagnosis with dural enhancement superiorly and laterally. (B) The radiation isodose colorwash dose distribution shows full coverage of the regions with local dural spread. (C) The first postradiation magnetic resonance imaging demonstrates diffuse leptomeningeal thickening.

Table 1: Dose prescriptions

Volume	Patient age (years)	Primary tumor size (cm)	Total dose (GyRBE)
PTV1-LN	Any	Any	36
PTV2-LN	Any	Any	50.4
PTV1-primary	any	< 5	36
PTV1-primary	≤ 3	any	36
PTV1-primary	> 3	5 -8	50.4
PTV1-primary	> 3	> 8	50.4
PTV2-primary	any	< 5	50.4
PTV2-primary	any	5 -8	55.8
PTV2-primary	any	> 8	59.4

*Early in this series, 2 patients were treated to nominal prescription doses of 46.8 and 48.6 GyRBE due to heterogeneity; however, >95% of the CTV received ≥47.9 GyRBE in both cases.

Table 2: Patient and disease characteristics

Characteristic		No. (%)
Sex		
	Female	12 (50%)
	Male	12 (50%)
Race		
	Black	4 (17%)
	White	19 (79%)
	Other	1 (4%)
Group		
	II	1 (4%)
	III	23 (96%)*
Stage		
	2	4 (17%)
	3	20 (83%)
Nodal status		
	Positive	8 (33%)
	Negative	16 (67%)
FOX fusion status		
	Positive	15 (63%)
	Negative	3 (12%)
	Unknown	6 (25%)
Intracranial extension		
	Present	13 (54%)
	Absent	11 (46%)
Primary site		
	Paranasal sinus	7 (29%)
	Infratemporal fossa	5 (21%)
	Nasal cavity	2 (8%)
	Nasopharynx	2 (8%)
	Orbit with skull base invasion	4 (17%)
	Parapharyngeal space	2 (8%)
	Pytergopalatine fossa	1 (4%)
	Middle ear	1 (4%)
Chemotherapy regimen		
	ARST0531	8 (33%)
	St Jude RMS 13	1 (4%)
	EpSSG RMS 2005	15 (63%)
Total Radiation Dose		
	41.4 GyRBE	3 (12%)

	45-50.4 GyRBE	11 (46%)
	55.8 GyRBE	9 (38%)
	59.4 GyRBE	1 (4%)

*One had R1 resection on delayed primary excision (DPE)

Table 3: Characteristics of patients who experienced treatment failure.

Age	Primary Site	ICE	Nodal Stage	Total Dose	Time to Failure (mo)	Type of Failure	Status
3	Infratemporal fossa	Yes	0	50.4	26	Local	Deceased
2	Sinus	No	0	50.4	6	Local	Deceased
2	Nasopharynx	No	0	50.4	7	Local	Deceased
2	Infratemporal fossa	No	0	55.8	12	Local	AWD
3	Infratemporal fossa	Yes	0	50.4	5	Local	Deceased
5	Parapharyngeal space	No	0	50.4	19	Local	NED
3	Nasal cavity	No	0	41.4	14	Regional	Deceased
12	Nasal cavity	Yes	1	46.8	4	Leptomeningeal	Deceased
3	Middle ear	Yes	1	48.6	2	Leptomeningeal	Deceased
18	Sinus	Yes	0	45	7	Leptomeningeal	Deceased
20	Sinus	Yes	1	55.8	3	Leptomeningeal	Deceased
10	Sinus	Yes	1	55.8	4	Leptomeningeal	Deceased
12	Orbit	Yes	1	55.8	5	Leptomeningeal	Deceased
14	Sinus	Yes	1	59.4	9	Brain parenchyma	Deceased

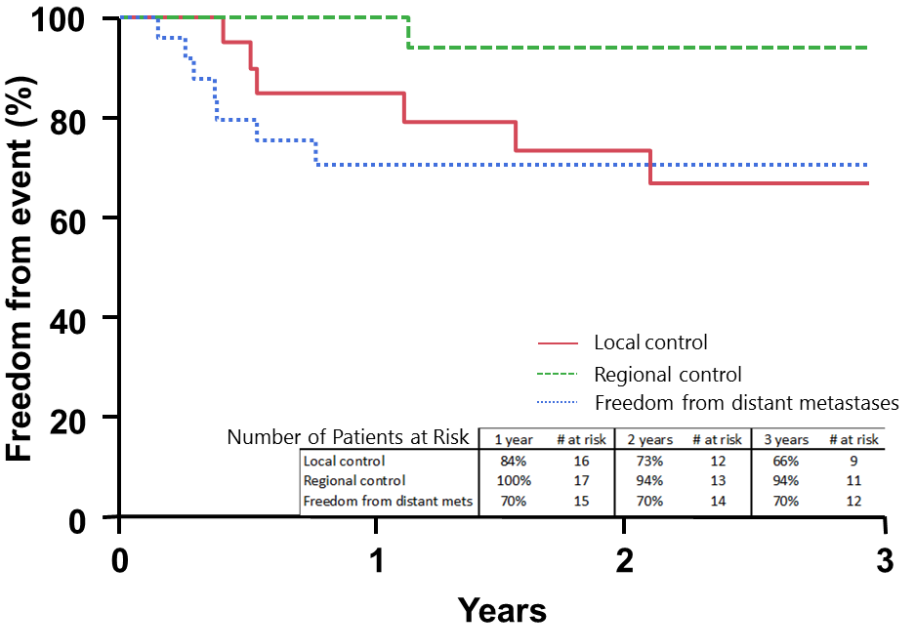
Abbreviations: AWD=Alive with disease; NED=No evidence of disease

Table 4: Univariate analysis of patient and tumor factors

Group		Local Control				Freedom from Metastases				Disease-free Survival				OS / CSS			
		3-year rate (%)	95% Confidence Interval		P value	3-year rate (%)	95% Confidence Interval		P value	3-year rate (%)	95% Confidence Interval		P value	3-year rate (%)	95% Confidence Interval		P value
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Age																	
	<4	56	28	81	0.22	**92**	61	99	**0.02**	43	20	70	0.53	68	20	70	0.83
	≥4	83	37	98		**45**	20	73		36	14	66		45	14	66	
Weeks from chemotherapy to RT																	
	<14	77	40	94	0.40	62	32	85	0.45	45	20	73	0.76	55	20	73	0.56
	≥14	56	25	82		82	49	95		36	14	66		64	14	66	
Elapsed days																	
	<39	67	27	92	0.82	71	33	93	0.91	29	7	67	0.48	43	7	67	0.24
	≥39	66	37	87		70	44	87		45	23	69		64	23	69	
Intracranial extension																	
	No	61	31	85	0.60	**100**	n/a	n/a	**0.0005**	51	23	78	0.14	**81**	23	78	**0.02**
	Yes	71	31	93		**45**	21	71		31	12	59		**38**	12	59	
Nodal (N) stage																	
	0	61	36	82	0.29	**94**	66	99	**< 0.0001**	**50**	27	73	**0.01**	**81**	27	73	**0.02**
	1	100	n/a	n/a		**19**	3	64		**19**	3	64		**38**	3	64	
Primary tumor size (cm)																	
	<5	75	38	94	0.79	**100**	0	0	**0.04**	60	25	87	0.20	73	25	87	0.53
	≥5	60	29	84		**56**	32	77		31	14	57		50	14	57	
Race																	
	White	67	40	86	0.94	79	55	92	0.12	46	25	68	0.23	62	25	68	0.30
	Other	67	15	96		40	10	80		20	3	69		40	3	69	
Sex																	
	Female	**90**	53	99	**0.05**	75	45	92	0.71	57	29	81	0.18	66	29	81	0.53

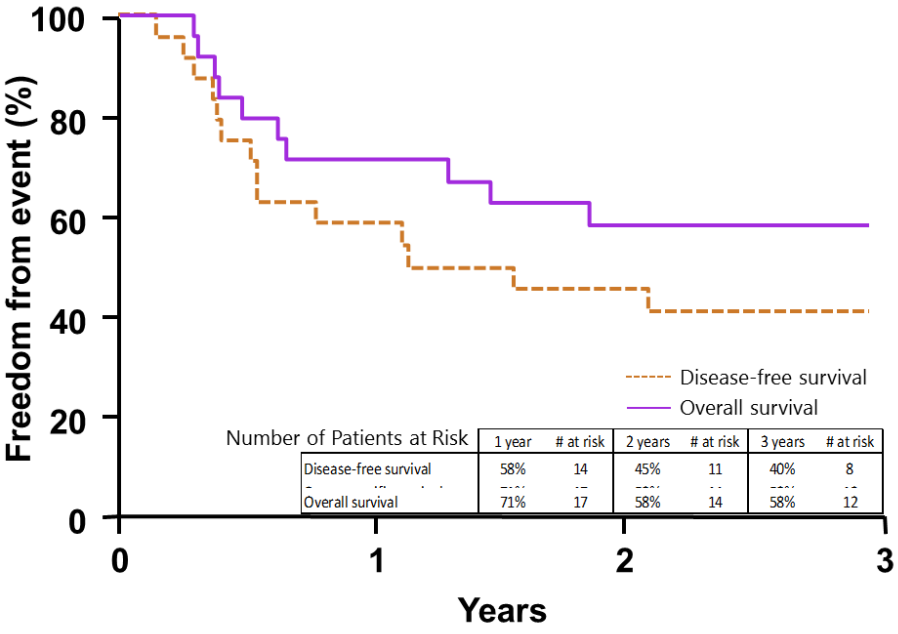
	Male	**42**	15	74		66	36	87		25	8	55		50	8	55	
Total dose																	
	<50.4	100	25	80	0.25	40	51	93	0.07	20	13	61	0.18	40	13	61	0.12
	≥50.4	60	42	98		78	30	84		46	22	78		62	22	78	

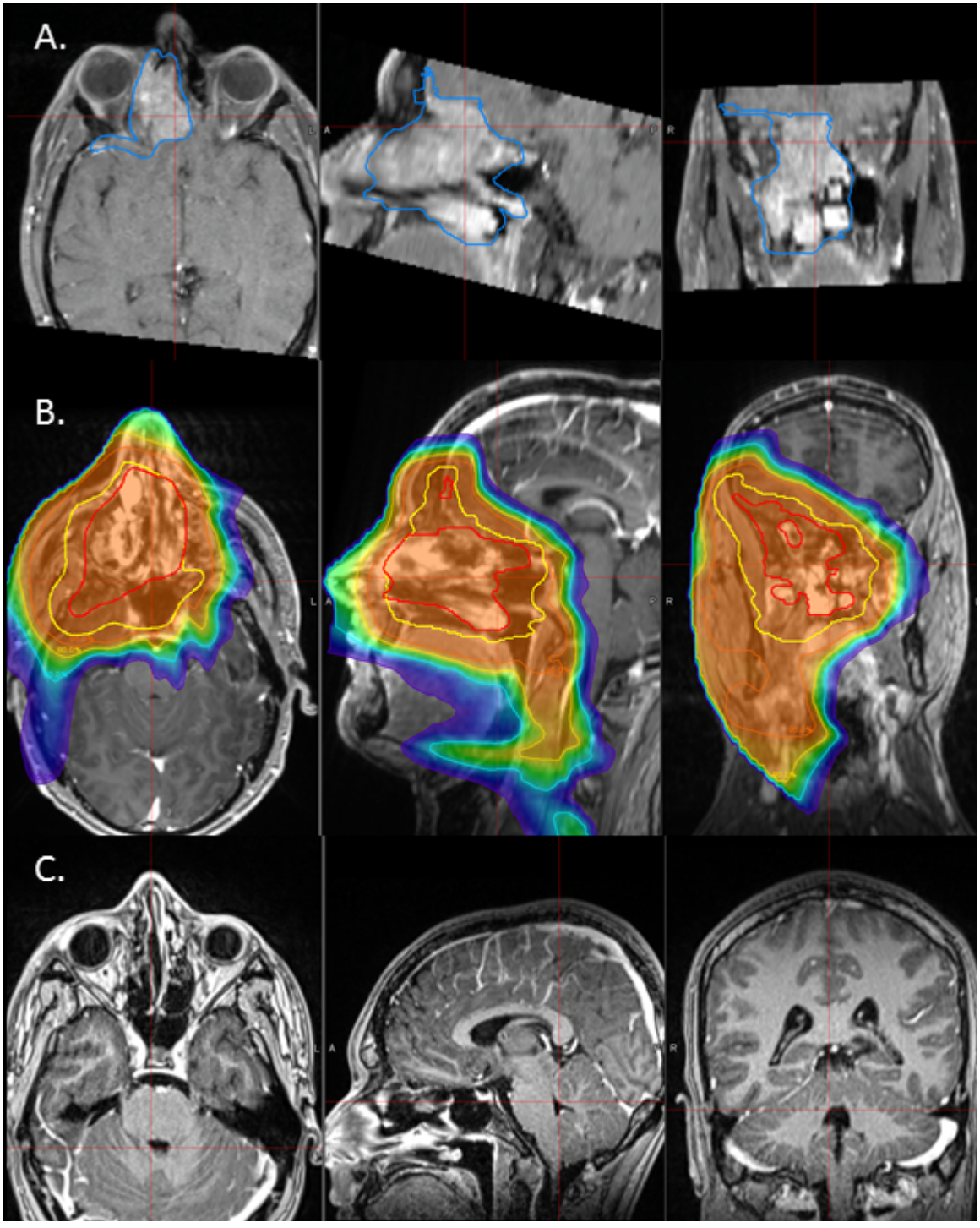
Abbreviations: RT=Radiation therapy; OS=Overall survival; CSS=Cause-specific survival; CI=Confidence interval
Note: Statistically significant values represented in bold



Number of Patients at Risk

	1 year	# at risk	2 years	# at risk	3 years	# at risk
Local control	84%	16	73%	12	66%	9
Regional control	100%	17	94%	13	94%	11
Freedom from distant mets	70%	15	70%	14	70%	12


100
80
60
40
20
0
Freedom from event (%)
0
1
2
3
Years
Disease-free survival
Overall survival
Number of Patients at Risk
1 year
at risk
2 years
at risk
3 years
at risk
Disease-free survival
58%
14
45%
11
40%
8
Overall survival
71%
17
58%
14
58%
12


A.
B.
C.