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Original Research Article

Radiation for ETMR: Literature review and case series of patients treated with proton therapy

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ABSTRACT

Background and purpose: Embryonal tumors with multilayered rosettes (ETMRs) are aggressive tumors that typically occur in young children. Radiation is often deferred or delayed for these patients due to late effects; proton therapy may mitigate some of these concerns. This study reviews the role of radiation in ETMR and describes initial results with proton therapy.

Materials and methods: Records of patients with embryonal tumor with abundant neuropil and true rosettes (ETANTR), medulloepithelioma (MEP), and ependymoblastoma (EPL) treated with proton therapy at our institution were retrospectively reviewed. A literature review of cases of CNS ETANTR, MEP, and EPL published since 1990 was also conducted.

Results: Seven patients were treated with proton therapy. Their median age at diagnosis was 33 months (range 10–57 months) and their median age at radiation start was 42 months (range 17–58 months). Their median overall survival (OS) was 16 months (range 8–64 months), with three patients surviving 36 months or longer. Five patients had disease progression prior to starting radiation; all 5 of these patients failed in the tumor bed. A search of the literature identified 204 cases of ETMR with a median OS of 10 months (range 0.03–161 months). Median OS of 18 long-term survivors (≥36 months) in the literature was 77 months (range 37–184 months). Of these 18 long-term survivors, 17 (94%) received radiotherapy as part of their initial treatment; 14 of them were treated with craniospinal irradiation.

Conclusions: Outcomes of patients with ETMR treated with proton therapy are encouraging compared to historical results. Further study of this rare tumor is warranted to better define the role of radiotherapy.

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1. Introduction

Embryonal tumors are highly malignant neoplasms with a propensity for spread along the craniospinal axis that primarily affect young children. In 2000, Eberhart [1], described a set of embryonal tumors with very poor prognosis occurring primarily in young children characterized by abundant neuropil and true "ependymoblastic" rosettes. These tumors became known as embryonal tumors with abundant neuropil and true rosettes (ETANTR).

ETANTR have unique molecular features, including 19q13.42 amplification (microRNA cluster C19MC) and LIN28A positivity, that are associated with tumorigenesis, aggressive behavior and poor survival [2–8]. Multiple groups have reported that ETANTRs, ependymoblastoma (EPL), and medulloepithelioma (MEP) comprise the same molecular entity characterized by normal INI-1 nuclear staining, LIN28A protein positivity, and C19MC microRNA cluster amplification at Chr19q13.41–42 [2,3,7–10]. The umbrella term, embryonal tumor with multilayered rosettes (ETMR), was suggested to encompass these entities [11]. In the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS), embryonal tumor with multilayered rosettes, C19MC-altered (ETMR) was added to the classification of CNS embryonal tumors [12].

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Patients with ETMR have a dismal prognosis [13,14]. Despite aggressive multi-modality intervention, median overall survival (OS) is 12 months or less, with a median age at diagnosis of 2 years or less [7,8].

Due to the rarity of these tumors, the optimal treatment approach has not been defined. Based on treatment of other embryonal tumors, an age-adapted multimodality approach is used, generally involving maximal safe resection, age and risk adapted radiotherapy, and chemotherapy. Emerging evidence in AT/RT, an aggressive embryonal tumor with similarly bleak OS, supports early radiation even in younger patients to improve disease control and long term-survival [15–19]. For patients at least 3 years of age, craniospinal irradiation (CSI) is often used given the propensity of these tumors to disseminate along the craniospinal axis.

Proton therapy has attracted significant interest in the treatment of pediatric malignancies due to its potential to decrease late effects and lower the risk of secondary malignancies [16]. In patients treated with craniospinal irradiation (CSI), the use of proton therapy compared to standard photon therapy effectively eliminates dose to the heart, lungs, and bowel [20–35].

The aim of this study was to evaluate a single institution experience in the use of proton therapy for the treatment of ETMR. We also reviewed the published peer-reviewed literature to evaluate the role of radiotherapy in the treatment of patients with ETMR.

2. Materials and methods

Most patients treated with proton therapy at MD Anderson Cancer Center (Houston, TX) are enrolled on a prospective registry protocol to study outcomes and normal tissue toxicities. We searched this database and identified patients with EPL, MEP, ETANTR, or ETMR treated with proton therapy. Their medical records were retrospectively reviewed for clinical data, treatment details, and outcomes. Pathology was reviewed at MD Anderson or Texas Children's Hospital before radiotherapy. All seven cases were evaluated by routine hematoxylin and eosin (H&E) stains and immunohistochemistry. The extent of surgical resection was defined as gross total resection (GTR, no residual tumor), near total resection (NTR, <10% residual tumor), subtotal resection (STR, >10% residual tumor), or biopsy only based on analysis of the postoperative MRI and intraoperative impression of the attending neurosurgeon. Patients underwent brain and spine MRI as well as CSF analysis prior to radiotherapy. Metastatic disease was staged according to modified Chang criteria [36].

All patients were treated with passive scatter proton therapy as previously described [16,37]. For craniospinal radiation (CSI), the brain was treated with opposed oblique fields and the spine was treated with two posterior-anterior fields. Junctions between fields were 1 cm apart and shifted every 4–5 fractions. The entire vertebral body was treated in all patients due to their young age. Doses were prescribed in cobalt-60 Gy equivalents (GyRBE) using a relative biological effectiveness value of 1.1 relative to photons per ICRU 78 [38]. All treatment was delivered at 1.8 GyRBE per fraction. The gross tumor volume (GTV) included the resection cavity and any residual disease as determined by imaging or neurosurgical impression. The clinical tumor volume (CTV) was defined by an anatomically constrained 1 cm volumetric expansion of the GTV. Planning and uncertainty margins were added for each beam as previously described [24]. All patients required anesthesia for simulation and treatment.

We used PubMed to search the published peer-reviewed literature. Search terms included EPL, MEP, ETANTR, ETMR, CNS, cerebrum, cerebral, and spine. EPLs and MEPs of the optic nerve, intraocular, pelvic, peripheral, and pre-sacral regions were excluded because of their molecular diversity compared with intracranial ETMRs[12] No language restrictions were used. All full-length articles were obtained and demographic, treatment, and survival data were gathered when available.

3. Results

3.1. MD Anderson cases

Details of patients treated with proton therapy at MD Anderson are summarized in Tables 1 and 2. Seven patients with ETMR were identified, 5 boys and 2 girls, with a median age at diagnosis of 33 months (range 10–57 months). The median age at radiation start was 42 months (range, 17–58 months). Six patients had infratentorial primary disease (86%) and one patient had a supratentorial tumor (14%). All seven patients had M0 disease at initial diagnosis, but one was M3 by the start of radiation (Pt. #5, Table 1).

Three patients had GTR, one had NTR, two had STR, and one had biopsy only. Six patients received chemotherapy after surgery and before radiation (Table 2). Chemotherapy was delivered according to various protocols as detailed in Table 2. Five patients had progressive disease (PD) before radiation (Table 1). All five of these patients progressed in the tumor bed; three also had distant CNS progression prior to radiation.

Two patients received focal radiation to the tumor bed (Pts. #6 and 7) to 50.4 GyRBE and 54 GyRBE. Five patients received CSI (Pts. 1–5), all to a dose of 36 GyRBE. For the patients who received CSI, the median dose to the primary tumor was 53.1 GyRBE (range, 45–55.8 GyRBE).

Table 1
Patient characteristics, treatments, and outcomes.

Pt #	Age at Dx (mo)	Gender	Location	Protocol	Stage	Surgery	Age at RT (mo)	PD before RT	CSI dose (GyRBE)	Tumor bed dose (GyRBE)	Site of recurrence after RT	Last status	OS from Dx (mo)
1	33	F	Left frontal lobe	SJYC07 [105]	M0	NTR	42	Local and distant	36	50.4		AWSD	64
2	33	F	Pons	Head Start III [106]	M0	STR	36	Local	36	54	Pons, spine	DOD	16
3	41	M	Pons	SJMB 03 [107]	M0	GTR	44	Local	36	55.8		DOC[1]	11
4	57	M	L-spine	ACNS 0332 [108]	M0	GTR	58	Local and distant	36	52.2		NED	44
5	26	M	CPA	None	M0	GTR	32	Local and distant	36	54 (PF), 45 (spine)		DOC[2]	13
6	49	M	Pons	ACNS 0332 [108]	M0	Bx	51	No	0	54		AWSD	8
7	10	M	CPA	CCG-99703 [109]	M0	STR	17	No	0	50.4		NED	36

Pt. # = Patient number, RT = radiotherapy, mo = months, PD = progressive disease, AWSD = alive with stable disease, DOD = died of disease, DOC = died of other or unknown cause, NED = no evidence of disease, Gy (RBE) = cobalt-60 Gy equivalents, CSI = craniospinal irradiation, GTR = gross total resection, NTR = near total resection, STR = subtotal resection, Bx = biopsy only, CPA = cerebellopontine angle, [1]unknown cause of death, [2]Patient was M3 at start of radiation with gross disease to the spine, died of cardiopulmonary arrest secondary to sepsis.

Table 2
Systemic therapy.

Pt. #	Protocol	Systemic therapy before RT	Systemic therapy with RT	Systemic therapy after RT
1	SJYC07 [105]	HDC×4 cycles with MTX, VCR, VLB, CYC and CDDP then TPT×2 cycles, followed by CYC maintenance	CDDP with VPA	Metronomic chemotherapy: VP-16, TMZ, VPA, CRA, MET, MLT×6 cycles
2	Head Start III [106]	CDDP, VP-16, VCR, CYC, and HD MTX followed by a cycle of VP-16, TMZ	None	MC (VPA, MLT, and MET) and VP-16, TMZ, CRA
3	SJMB 03 [107]	VCR, CDDP, and CYC×2 cycles	None	None
4	ACNS 0332 [108]	None	VCR and CDDP	HD CDDP, VCR, CYC[1] with ASCT. Switched to MC (ISO, MET, MLT, VPA, VP-16, TMZ, CRA, CYC, and celecoxib)
5	None	IFO, VP-16, and VCR×3 cycles	None	2× cycles HD CDDP/THIO with ASCT
6	ACNS 0332 [108]	Vorinostat, CRA	CDDP and VCR	None
7	CCG-99703 [109]	CDDP, VCR, CYC, VP-16×3 cycles, then CDDP/THIO×3 cycles followed by SCT	None	None

Pt. # = Patient number, RT = radiotherapy, ASCT = autologous stem cell transplant, [1]aborted due to hearing loss with cisplatin, HDC = high dose chemotherapy, MC = metronomic chemotherapy, MTX = methotrexate, VCR = vincristine, VLB = vinblastine, CYC = cyclophosphamide, CDDP = cisplatin, TPT = topotecan, VPA = valproic acid, VP-16 = etoposide, TMZ = temozolomide, CRA = cis-retinoic acid, MET = metformin, MLT = melatonin, ISO = isotretinoin, IFO = ifosfamide, THIO = thiotepa (THIO).

Radiation was well tolerated with minimal acute toxicities. Regarding long term toxicities, two patients developed endocrinopathies. One patient remained within the lowest 25% quartile of stature for his age with borderline normal IGF-1 (Pt. #7, not yet on growth hormone therapy) by 2.5 years after completing therapy, and one patient required cortisol replacement therapy 53 months after proton therapy (Pt. #1).

The median follow-up was 40 months for surviving patients. At a median OS of 16 months (range, 8–64 months) for all patients, four of seven patients (57%, crude rate) were alive without evidence of disease progression, and three patients (43%, crude rate) died. The causes of death for these three patients were cardiac arrest due to sepsis during chemotherapy after radiotherapy, disease progression, and unknown.

3.2. Review of the literature

ETMRs have been reported in the literature as EPL, MEP, and ETANTR. Due to the rarity of these tumors, descriptions are often found in individual case reports or small case series in the literature. Since the first report of ETANTR in 2000 [1], some ETMRs were reported as EPL and MEP. This review focuses on MEP, EPL, and ETANTR of the CNS. Cases of MEP and EPL outside the CNS were excluded; these included cases with primary sites in the ovary [39,40], sacrococcygeal region [41,42], pelvis [43,44], optic nerve [45,46], intraocular [47], and sciatic nerve [48].

A search of the peer reviewed literature published since 1990 yielded 204 cases of ETMR. Other authors have reviewed cases of MEP and EPL described since the 1920s to 1990 [45,49–51]. The patient characteristics, treatment, and outcome of these 204 cases plus the seven MD Anderson cases are summarized in Table 3 [1,5,7,9,14,49–98].

For all 211 reported cases, the female: male ratio was 1.08:1. The majority of tumors were supratentorial (62%). The most commonly involved primary sites were the frontal lobe, cerebellum, and brainstem. Less commonly, cases involved the parietal lobe, temporal lobe, occipital lobe, pineal region, sella turcica, basal ganglia, thalamus, 4th ventricle, 3rd ventricle, lateral ventricles, and spine.

The median age at presentation was 27.6 months (range 0.5–216 months). Symptoms depended on the location of the tumor and included headache, vomiting, cranial nerve deficits, ataxia, weakness and paralysis. Likewise, imaging characteristics were variable. Tumors were often solid with cystic and calcified components with or without enhancing portions on post-contrast imaging. Metastatic stage was not reported in 96 cases (45.5%). In the 115 cases where M-stage was available, 87 (76%) patients had M0 disease, 6 (5%) had M1 disease, 3 (3%) had M2 disease, and 19 (17%) had M3 disease (Table 3).

The most common treatment was a trimodality approach with surgery, chemotherapy, and radiation (56 of 211 patients, 26.5%). The extent of resection was reported as GTR in 54 cases, NTR in 6 cases, STR in 57 cases, and unknown in 53 cases; 3 patients did not receive any treatment, 21 cases (10%) did not report treatment, and 17 patients received biopsy only. Most patients, 156 of 211 (74%) received chemotherapy (Table 3).

Sixty-five of 211 (31%) patients received radiation, which was typically avoided in patients less than three years old. The majority of patients in the literature were treated with photons. Two patients in the literature were treated craniospinal proton therapy [9,68].

Follow up information was available for 178 patients. Median OS was 10 months after initial diagnosis (range 0.03–183.9). At last follow up, 123 (69%) were dead and 55 (31%) were alive. The resection cavity was the most common site of disease recurrence, followed by the spine, which is consistent with the patterns of failure of PNETs [99,100].

Only 18 patients have been reported who are long-term survivors (≥36 months) with a median age at diagnosis of 35.4 months (range 7–139.2 months), and a median OS of 77.25 months (range 37.2–183.9 months) [7,50,55,66,67,69,78,80]. Sixteen of these eighteen patients received trimodality therapy with surgery, chemotherapy and radiotherapy; one patient received surgery and chemotherapy [55], and one received surgery and radiation [69]. Therefore, 94% of long-term survivors (17 of 18) in the literature received radiotherapy as part of their primary treatment [55]. Fourteen of these patients received CSI with tumor bed boost, one received local radiation only, and two had unknown radiation treatment volumes. Treatment and outcomes of long-term survivors from the literature are summarized in Table 4.

4. Discussion

This report summarizes treatments and outcomes of 211 patients with ETMR described since 1990. This is the largest series focusing on the use of radiotherapy in ETMR, and the only series detailing long-term survivors treated with proton therapy. Our review suggests that the use of early radiotherapy in ETMR may contribute to long-term survival. Of 18 long-term survivors in the literature, 17 received radiotherapy as part of their treatment (Table 4). Of seven patients treated at MD Anderson with proton

Table 3
Patient characteristics, treatment, and outcomes of ETMR (ETANTR, MEP, EPBL) cases described in the literature.

	No (%) TOTAL	No (%) EPBL	No (%) MEP	No (%) ETANTR
Age (months)				
0–12	29 (14)	4 (13)	5 (20)	20 (12.9)
>12–24	68 (32)	6 (19)	7 (28)	55 (35.5)
>24–36	55 (26)	9 (29)	5 (20)	41 (26.5)
>36–48	35 (16.6)	6 (19)	3 (12)	26 (16.8)
>48–60	10 (4.8)	2 (7)	2 (8)	6 (3.8)
>60	14 (6.6)	4 (13)	3 (12)	7 (4.5)
Gender				
Males	97 (46)	20 (65)	12 (48)	65 (42)
Females	105 (50)	10 (32)	5 (20)	90 (58)
Unreported	9 (4)	1 (3)	8 (32)	0
Primary tumor location				
Supra-tentorial	130 (61.6)	16 (52)	17 (68)	97 (62.6)
Infra-tentorial	73 (34.6)	14 (45)	7 (28)	52 (33.5)
Supra and Infra-tentorial	4 (1.9)	0	1 (4)	3 (1.95)
Unreported	4 (1.9)	1 (3)	0	3 (1.95)
M Stage				
MX	96 (45.5)	11 (35.2)	11 (44)	74 (47.7)
M0	87 (41.2)	17 (54.8)	9 (36)	61 (39.4)
M1	6 (3)	1 (3.33)	4 (16)	1 (0.65)
M2	3 (1.5)	1 (3.33)	1 (4)	1 (0.65)
M3	19 (8.8)	1 (3.33)	0	18 (11.6)
M4	0	0	0	0
Initial treatment				
None	3 (1.4)	0	3 (12)	0
Surgery (S)	35 (16.6)	7 (22)	8 (32)	20 (12.9)
Chemotherapy (C)	9 (4.3)	0	0	9 (5.8)
Radiotherapy (RT)	1 (0.4)	0	1 (4)	0
S, C	78 (37)	10 (32)	4 (16)	64 (41.3)
S, RT	3 (1.4)	1 (5)	0	2 (1.3)
RT, C	5 (2.4)	0	1 (4)	4 (2.7)
S, C, RT	56 (26.5)	7 (22)	7 (28)	42 (27)
Unknown	21 (10)	6 (19)	1 (4)	14 (9)
Outcome (n = 178)				
Unknown*	33*	6	2	25
Mean survival time	19.3 (median 10, 0.03–183.9 range)	22.5	19.7	18.7
Alive	55 (30.9)	6 (24)	4 (17)	45 (34.6)
Dead	123 (69.1)	19 (76)	19 (83)	85 (65.4)
DOD	117 (65.7)	17 (68)	16 (70)	84 (64.6)
DOC	6 (3.4)	2 (8)	3 (13)	1 (0.8)
NED	27 (15.2)	4 (16)	1 (4)	22 (16.9)
RPD	10 (5.6)	0	0	10 (7.7)
AWSD	18 (10.1)	2 (8)	3 (13)	13 (10)

Table includes the 7 cases treated at MD Anderson. S = surgery, C = chemotherapy, RT = radiotherapy, DOD = died of disease, DOC = died of other, NED = no evidence of disease, AWSD = alive with stable disease, RPD = recurrent progressive disease, *33 cases did not report outcome, not included in percentage calculation. Compiled from references: [1,5,7,9,14,49–98].

therapy, three survived 36 months or longer from diagnosis (Table 1).

Multiple authors have reported a statistically significant OS benefit in ETMR with the addition of radiotherapy. Alexiou et al. [55] reported that ETANTR patients treated with radiotherapy had a statistically significant improved OS compared to patients who did not receive radiotherapy. Similarly, Ding [49] found that the addition of radiotherapy, chemotherapy or combined chemo-radiotherapy had a significant survival benefit compared to patients who did not receive radiotherapy, chemotherapy or combined post-operative chemo-radiotherapy. Horwitz reported a statistically significant OS benefit on multivariate analysis of patients who received complete surgical resection, radiotherapy and high dose chemotherapy [69]. In a series of 11 EPL patients treated on the prospective HIT-trials [66], the only two long-term survivors (follow up of 12.7 and 9.4 years, respectively) received CSI therapy with involved field boost as part of their first line-therapy; a third patient who received radiation had stable disease at 2.3 years.

Due to the very young patient population of ETMR, with a median age at diagnosis of 2 years, there is often hesitation to administer radiotherapy due to concern for late effects. There is considerable interest in using proton therapy to reduce unnecessary radiation exposure compared to photon-based radiotherapy. For patients treated with CSI, the use of proton therapy reduces acute hematologic and gastrointestinal side effects [101]. For patients treated with focal fields in the brain or spine, proton therapy decreases the low-dose exposure of adjacent, uninvolved brain parenchyma and spinal cord. By minimizing radiation dose to critical structures such as the hippocampi and hypothalamus, proton therapy may decrease the risk of late effects, including endocrine deficiencies [102] and secondary malignancies [16,37]. In particular, the use of proton therapy may decrease neurocognitive deficits in patients treated with focal radiation fields [103,104]. The youngest patient treated in our institutional series was 17 months old at the time of radiotherapy and was alive without evidence of disease recurrence 36 months after diagnosis (Pt. #7).

Optimal radiation volumes remain poorly defined in ETMR. In our institutional series, all seven patients had M0 disease at diagnosis; five of these patients developed recurrence within the resection cavity and three of those five patients had CNS spread in 1–11 months prior to radiation. Based on the North American approach to other embryonal tumors, CSI may be considered for

Table 4
Treatment and outcomes of long Term Survivors (≥36 months) in literature.

Age (mo)	Loc.	Treatment	XRT details	Chemo	Outcome	OS	Ref
15	C	S (GTR), C, RT	20 Gy CSI + 26 Gy TBB	IT MTX×3	NED	161	[50]
17	RTP	S (GTR), C, RT	55 Gy LF	VCR, VP-16, CDDP, CYC, CP	NED	44	[50]
36	LF	S, C, RT	Unknown	Unknown	NED	42	[1,67]
67.2	LFT	S (GTR), C, RT	35.2 Gy CSI, 20 Gy TBB	Per HIT91	NED	152.4	[66]
40.8	LP	S (GTR), C, RT	35.2 Gy CSI, 20 Gy TBB	Per HIT91	NED	112.8	[66]
67.2	RFP	S (GTR), C, RT	36 Gy CSI, 30 Gy TBB	Per HIT SKK2000	DOD	37.2	[66]
48	RP	S (GTR), C, RT	35.8 Gy CSI, 19.9 Gy TBB	CP, VCR, CYC, CDDP	NED	84	[78]
7	LTP	S (GTR), C	None	VCR, CDDP, VP-16, CYC, MTX	NED	48	[55]
23	ST	S, C, RT	Unknown	Unknown	Alive	56	[7]
138	ST	S (GTR), RT	CSI + TBB[1]	None	NED	183.9	[69]
34.8	SC	S (GTR), C, RT	CSI + TBB[1]	VPCP×2, HDC	NED	43.2	[69]
26.4	ST	S (GTR), C, RT	CSI + TBB[1]	VPCP×2, HDC	NED	143.6	[69]
38.4	ST	S (STR), C, RT	CSI + TBB[1]	VPCP×2, HDC	AWSD	90.9	[69]
81.6	ST	S (GTR), C, RT	CSI + TBB[1]	VPCP×2, MP + CDDP×2	NED	63.8	[69]
24	ST	S (STR), C, RT	CSI + TBB[1]	VPCP×2, MP×2, THIO×2	NED	143.4	[69]
31.2	ITE	S (GTR), C, RT	CSI + TBB[1]	VPCP×2, HCD	NED	103.3	[69]
139.2	ITE	S, C, RT	CSI + TBB[1]	VPCP×2, THIO×2, TMZ×2	NED	70.5	[69]
24	LC, LO	S (GTR), C, RT	32 Gy CSI, 24 Gy TBB	HRP + IT VCR, CDDP, VP-16	NED	52	[80]

S = surgery, C = chemotherapy, RT = radiotherapy, CSI = craniospinal irradiation, GTR = gross total resection, STR = subtotal resection, TBB = tumor bed boost, LF = local field, NED = no evidence of disease, DOD = died of disease, AWSD = alive with stable disease, IT = intrathecal, R = right, L = left, T = Temporal, P = parietal, F = frontal, C = cerebellum, O = occipital, ST = supratentorial, ITE = infratentorial, SC = spinal cord, MP = melphalan, VP-16 = etoposide, THIO = thiotepa, VPCP = VP-16 + CP, CP = carboplatin, CDDP = cisplatin, VCR = vincristine, CYC = cyclophosphamide, TMZ = temozolomide, HDC = MP + CDDP + THIO, HRP = 2× VCR + CYC + VP-16 → 2× VCR + CP + VP-16 → 2× VCR + CDDP + VP-16 → IT triplet ×7, ? = unspecified, [1] per protocol in Ref. [110].

patients older than three years of age. Notably, the European approach to AT/RT on the current EU-RHAB protocols includes focal radiation for patients with M0 disease. Results from the St. Jude's and COG trials in AT/RT are awaited to better define radiation volumes in these young patients with very aggressive CNS embryonal tumors.

5. Conclusions

ETMR is an aggressive embryonal tumor occurring in young children with a historic OS of 10 months. Based on the treatment of other CNS embryonal tumors, the treatment of ETMR typically consists of maximal safe surgery, chemotherapy and radiotherapy. Due to the very young age of these patients, radiation is often delayed or avoided. This comprehensive literature review and our institutional experience suggest that early radiotherapy may improve outcomes in ETMR. The use of proton therapy to reduce acute and long term effects may facilitate the use of radiation in these young patients.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2018.11.002.

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