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Outcomes in lung-only metastatic rhabdomyosarcoma: An analysis of data from the European paediatric Soft tissue sarcoma Study Group MTS 2008 study

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ABSTRACT

Purpose: Patients with metastatic rhabdomyosarcoma (MTS RMS) and lung as the only metastatic site have better reported outcomes than other patients with MTS RMS. We analysed patients with lung-only MTS RMS receiving standard treatment within the EpSSG MTS 2008 protocol.

Patients and methods: Previously untreated patients aged < 21 years with MTS RMS received standard induction chemotherapy with radiotherapy (RT) and/or surgery to the primary site and RT recommended to all metastatic sites. Clinical characteristics, treatment and outcomes of patients with lung-only MTS RMS were compared to lung + other site and other site MTS RMS.

Results: Among 270 patients with MTS RMS, 59 (22%) had lung-only metastatic disease, 68 (25%) in lung + other and 143 (53%) in other sites. 3-yr Event Free Survival (EFS) and Overall Survival (OS) for lung-only MTS RMS were 40% (95%CI 27–53%) and 60% (95%CI 46–71%). Although 3-yr OS for lung-only MTS RMS was significantly better than lung + other (35%; 95% CI 24–47%) and other (49%; 95% CI 40–57%) sites (p = 0.0382), EFS and OS adjusted for known clinical (Oberlin) risk factors, did not differ between the groups. 3-year EFS was significantly higher in patients with lung-only MTS who received RT to the lungs (RT, n = 26, EFS 56%, 95% CI 35–73%; no RT, n = 24, EFS 33%, 95% CI 16–52%, p = 0.0435).

Conclusions: Better outcomes for lung-only MTS RMS seem to be determined by the presence of fewer clinical risk factors. Whole lung radiotherapy continues to be recommended in patients with lung-only MTS RMS.

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1. Introduction

Around 15% of young patients with rhabdomyosarcoma (RMS) have metastatic disease (MTS) at presentation [1,2], with poor prognosis and little improvement in survival over the last 30 years [2–10]. Lung, the commonest site of metastasis, is the only metastatic site in 18–24% of MTS RMS [2,11]. These patients have better outcomes compared to the whole metastatic group [2,3,12,13].

In a pooled analysis including 788 patients with MTS RMS, 4 key clinical (Oberlin) risk factors associated with adverse outcome were identified: 1. more than 2 metastatic site; 2. age < 1 or ≥ 10 years; 3. unfavourable primary tumour site (defined as extremity or 'other site') and 4. bone/bone marrow involvement [11]. Patients with no Oberlin risk factors had 50% 3-yr EFS, reducing as the number of risk factors increased to only 5% if all 4 Oberlin risk factors were present. Lung-only MTS RMS patients by definition can have no more than 2 risk factors (i.e. unfavourable age and primary site).

The European *paediatric* Soft tissue sarcoma Study Group (E*p*SSG) collected data on patients with MTS RMS treated within the MTS 2008 amendment of the RMS 2005 protocol. The overall outcomes of this patient group are reported elsewhere [14]. Here we report the clinical features, management and outcomes by Oberlin risk factors and use of lung RT for patients with lung-only MTS RMS, comparing with lung + other and other MTS RMS treated within the E*p*SSG MTS 2008 study.

2. Methods

2.1. Patients

Patients with metastatic RMS were registered into the MTS 2008 amendment of the E*p*SSG RMS 2005 protocol (NCT NCT00379457) between September 2008-December 2016 [14]. The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), national regulatory authorities and relevant ethical committees. Written informed consent was obtained from patients and/or their parents or legal guardians. All data were anonymised.

2.2. Diagnosis and staging

Patients underwent primary diagnostic biopsy/surgery and staging investigations according to protocol. Pulmonary metastatic disease was

Table 1
Patient distribution by clinical characteristics.

	Lung-only n = 59	Lung + other n = 68	Other n = 143	Total n = 270	%	Chi-square test p-value
Gender						
Male	35	43	73	151	55.9	0.2091
Female	24	25	70	119	44.1	
Median age, years	7.05	9.13	10.4	9.64		
(range)	(0.71–18.81)	(1.56–19.50)	(0.07–20.82)	(0.07–20.82)		
Age at diagnosis						
≤ 1 or ≥ 10 years	19 (32.2%)	32 (47.1%)	81 (56.6%)	132	48.9	**0.0064**
1–9 years	40 (67.8%)	36 (52.9%)	62 (43.4%)	138	51.1	
Histology						
Alveolar RMS	13	37	93	143	53.0	**<0.0001**
Botryoid RMS	2	1	1	4	1.5	
Embryonal RMS	42	23	43	108	40.0	
Not Otherwise Specify RMS	1	4	6	11	4.0	
Spindle cells/Leiomyomatous RMS	1	3	–	4	1.5	
Histology						
Favourable	45	27	44	116	43.0	**<0.0001**
Unfavourable	14	41	99	154	57.0	
Primary tumour (PT) site						
HN non PM	3	3	6	12	4.4	0.3442
HN PM	19	12	32	63	23.3	
GU BP	10	7	11	28	10.4	
GU non BP	4	6	8	18	6.7	
Extremities	8	18	41	67	24.8	
Other sites	15	21	41	77	28.5	
Unknown[a]	–	1	4	5	1.9	
PT site by Oberlin						
Favourable	36	28	57	121	44.8	**0.0179**
Unfavourable	23	40	86	149	55.2	
Tumour size						
a: ≤ 5 cm	13	11	33	57	21.1	0.4283[b]
b: > 5 cm	45	56	102	203	75.2	
x: not evaluable	1	1	8	10	3.7	
T-invasiveness						
T1	14	18	37	69	25.6	0.8922[b]
T2	45	49	101	195	72.2	
T0/Tx	–	1	5	6	2.2	
Loco-regional N						
N0	42	27	34	103	38.2	**<0.0001**[b]
N1	17	40	105	162	60.0	
Nx	–	1	4	5	1.9	
No. of metastatic lesions						
Single lesion	14	–	13	27	10.0	**<0.0001**
Multiple lesions	45	68	130	243	90.0	

[a] Origin of tumour is undetectable.
[b] The association between each variable and lung metastasis involvement has been tested excluding patients with not evaluable size, nodal status unknown (Nx), T0 or Tx (invasiveness unknown).

defined per protocol as computed tomography scan evidence of ≥ 1 pulmonary nodule of ≥ 10 mm diameter *or* ≥ 2 well-defined nodules of 5–10 mm diameter *or* ≥ 5 well-defined nodules < 5 mm [14]. Unfavourable primary disease sites were defined as extremities, "other" and unknown. All head and neck and genitourinary sites were considered favourable [11].

2.3. Treatment

Induction chemotherapy included nine 21-day cycles of chemotherapy: four cycles of IVADo (ifosfamide, vincristine, actinomycin-D, and doxorubicin) followed by five cycles of IVA. Maintenance chemotherapy comprised twelve 28-day cycles of low-dose cyclophosphamide and vinorelbine [13]. Surgical resection of the primary tumour was recommended for patients not in complete remission (CR) post cycle 6 of induction chemotherapy where feasible and non-mutilating. Surgical resection of metastases was at the discretion of the clinical team.

Radiotherapy (RT) was recommended wherever possible to the primary tumour site, involved locoregional lymph node sites and all metastatic sites after recovery from surgery, beginning with chemotherapy cycle 7 [14]. The recommended dose to the whole lung was 15 Gy in 10 fractions.

2.4. Reassessment and follow up

Tumour reassessment was undertaken every 3 cycles of induction therapy and every 3 months on maintenance chemotherapy using three-dimensional tumour volume calculations. Primary tumour response was measured by volume reduction; response of metastatic lesions was measured according to the Response Evaluation Criteria in Solid Tumours (RECIST v1.0) (14, Supplementary Table 1). Follow-up imaging of the primary site and chest x-ray was recommended post-treatment [15].

2.5. Statistical methods

Differences between distribution of categorical variables were investigated using the Chi-square or Fisher's exact test, depending on frequency distribution. Survival probabilities were estimated using the Kaplan-Meier method and heterogeneity among strata of each variable was analysed using the log-rank test. Event free survival (EFS) was calculated from the date of diagnosis to the time of disease progression, recurrence, refusal of therapy, treatment suspension due to toxicity or death due to any cause. Overall survival (OS) was defined as time from diagnosis to death from any cause. Patients still alive or lost to follow-up were censored at the date of last observation. Survival multivariable analysis using Cox proportional hazard model was conducted to investigate the impact of variables with $p < 0.25$ at univariate analysis.

All data analyses were performed using SAS statistical package (SAS, release 9.4; SAS Institute Inc., Cary, NC, USA). To avoid survivor bias, analysis of the impact of lung RT included only patients alive without disease progression at Day 221 (the latest timepoint at which local therapy would be expected to have commenced) [16]: patients who commenced RT after Day 221 were considered as non-irradiated [16].

3. Results

3.1. Patient characteristics

Among 270 patients with MTS RMS registered in the MTS 2008 study, 59 (22%) had lung-only metastatic disease, 68 (25%) had metastatic lesions in the lung + other sites and 143 (53%) had metastatic lesions only in non-lung (other) sites. Of 59 lung-only patients, 38 (64%) had bilateral involvement and the majority (45/59, 76%) had multiple (> 1) lung lesions (Table 1). Lung was the commonest single metastatic organ site in MTS RMS (59/127, 46%; Supplementary Table 2). Patients with lung-only metastases were significantly more likely to be aged between 1 and 10 years (40/59, 68%, $p = 0.006$), have favourable histology (45/59, 76%, $p < 0.0001$), no locoregional lymph node involvement (42/59, 71%, $p < 0.0001$) and single metastatic lesions (14/59, 24%, $p < 0.0001$).

3.2. Treatment

Treatment is summarised in Supplementary Table 3. Key findings were that patients with lung-only MTS RMS were significantly less likely to have delayed surgery to primary site (73% versus 88%, $p = 0.0068$) or metastatic sites (8% versus 23%, $p = 0.040$), more likely to have radiotherapy to metastatic sites (55% versus 43%, $p = 0.048$), had similar rates of completing standard chemotherapy (86% versus 84%, $p = 0.720$) and significantly higher rates of completing maintenance chemotherapy (73% versus 57%, $p = 0.024$).

Forty-eight patients (84%) received RT, with information on RT target available in 47/48. Nine (16%) were not irradiated (see Supplementary Table 3). In 2 cases data on whether patients received RT were missing. The description of irradiated site(s) was available for 45/46 patients irradiated ≤ Day 221 (Supplementary Table 4).

Lung RT at a median dose of 15.0 Gy (IQR 14.4–15.0 Gy) was given before Day 221 to 26/57 (46%) of lung-only MTS patients with available data. Twenty four patients did not receive lung RT before Day 221 (19 to a site other than lungs, 2 to lungs > Day 221 and 3 no RT and no event before Day 221). The proportion of patients receiving lung radiotherapy was not significantly different whether lung metastases were unilateral or bilateral (11/20 v 15/37; $p = 0.30$), single or multiple (6/13 v 20/44; $p = 0.96$), nor whether disease status after cycle 6 of induction treatment was CR or non-CR (12/24 v 6/16; $p = 0.44$). Clinical features did not differ significantly between lung-only patients who did or did not receive RT (data not shown) nor between lung-only MTS patients who did or did not receive RT to the lungs (Supplementary Table 5).

3.3. Response to treatment

Response at the primary tumour site following 3–4 cycles of induction chemotherapy was available for 53/59 patients (90%), with 47/53 (89%) achieving a response better than Stable Disease. Among 51 patients with lung assessment, 19 (37%) achieved lung CR (2 unknown). Following cycle 6, 24/40 (60%) patients with available data were in lung CR and 13/40 (32%) were in CR at all sites. By end of treatment 43/59 (73%) patients achieved lung CR and 32/59 (54%) of patients achieved CR at all sites.

3.4. Outcomes

Outcome data were available for 58/59 (98%) lung-only MTS patients. Median follow up of alive patients ($n = 29$) was 59.1 months (range 24.4–110.7). The 3-yr EFS was 40% (95%CI 27–53%) and 3-yr OS was 60% (95%CI 46–71%). There was no difference in outcome for single versus multiple lung lesions (EFS 34 vs 42%, $p = 0.98$; OS 77 vs 55%, $p = 0.70$). Univariable analysis of EFS and OS by gender, age at diagnosis (both < 10 v ≥ 10 years and ≤ 1 or ≥ 10 years v 1–10 years were compared), histology, tumour site, tumour size, T-invasiveness and locoregional lymph node involvement unexpectedly showed tumour size ≥ 5 cm as associated with improved OS (3-yr OS 64% (95% CI 44–71%) vs 40% (95% CI 14–66%), $p = 0.0398$ but this was not confirmed in multivariable analysis (data not shown).

Thirty-five patients (60%) experienced an event (Supplementary Table 5) after a median time from diagnosis of 14.2 months (range 1.5–63.8). Five events occurred during and 3 after completing standard induction chemotherapy, 14 during maintenance therapy and 13 off therapy. At last follow-up, 4/35 patients were alive in 2nd CR off therapy, 2 were alive with disease and 28 had died.

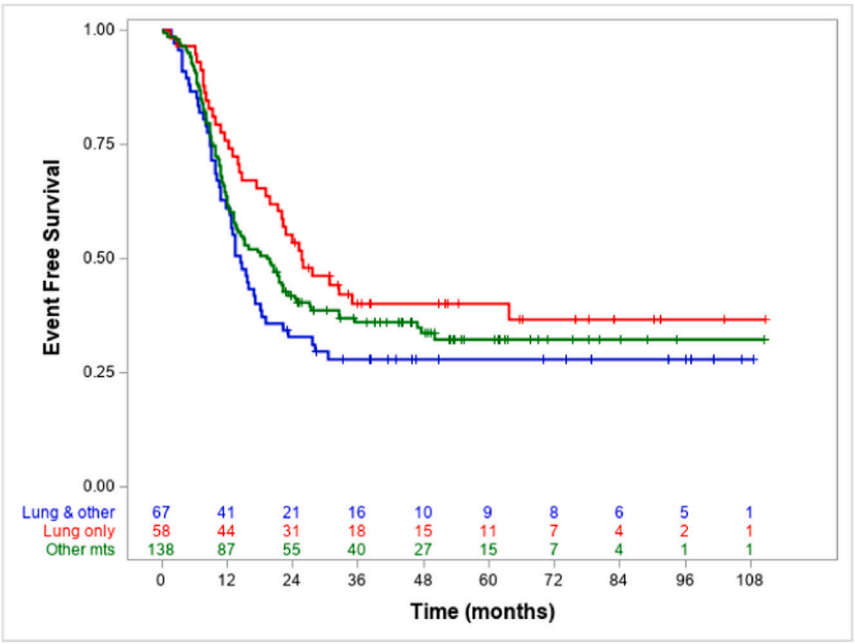
OS but not EFS for lung-only MTS RMS was significantly better than lung + other and other sites ($p = 0.0382$, Fig. 1a and b) and compared to all other patients with MTS RMS ($p = 0.0356$, Supplementary Fig. 1a and b).

Among patients with a single metastatic site, lung-only or bone/bone marrow only sites had inferior outcomes compared to all other single metastatic sites (EFS p = 0.0004, OS p = 0.0002, Fig. 2a and b) of which the majority (19/34) had distant lymph node involvement.

Patients for whom lung was the only metastatic site had significantly fewer Oberlin risk factors than patients with lung + other or other metastatic sites (Table 2, p < 0.0001) and fewer risk factors than other patients with a single metastatic site (Table 3, p < 0.0001). When adjusted for the presence of 0, 1, or 2 Oberlin risk factors, EFS and OS did not differ between lung-only, lung + other and other groups (Supplementary Table 6).

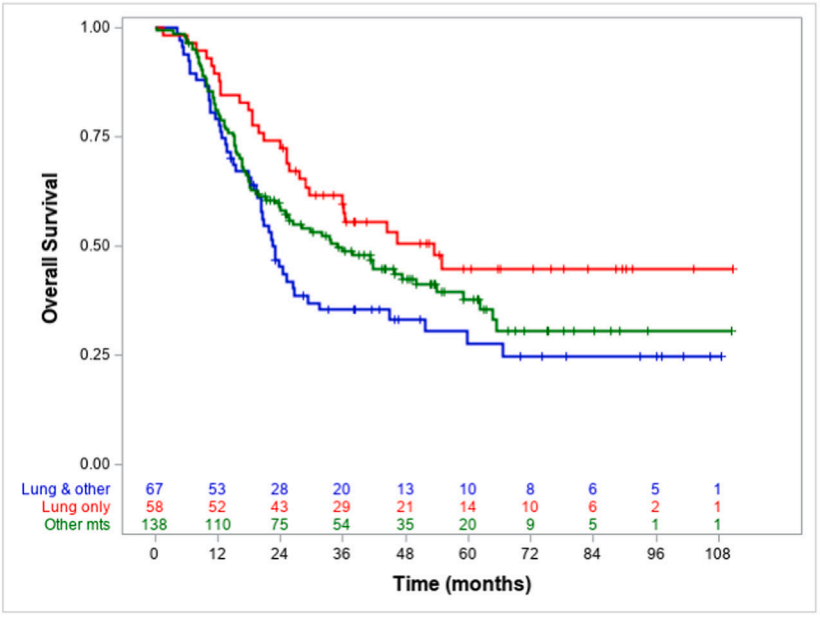
3-year EFS but not OS was significantly higher in patients with lung-only MTS who received RT to the lungs (EFS: RT 56%, 95%CI 35–73%

a



	N	Failed	3-yr EFS (CI 95%)	p-value
Lung-only	58	35	40.2 (27.3-52.7)	0.1582
Lung + other	67	48	28.0 (17.8-39.1)	
Other mts	138	90	36.2 (28.1-44.3)	

b



	N	Deaths	3-yr OS (CI 95%)	p-value
Lung-only	58	29	59.7 (45.8-71.1)	0.0382
Lung + other	67	46	35.4 (23.9-47.0)	
Other mts	138	80	48.9 (40.0-57.1)	

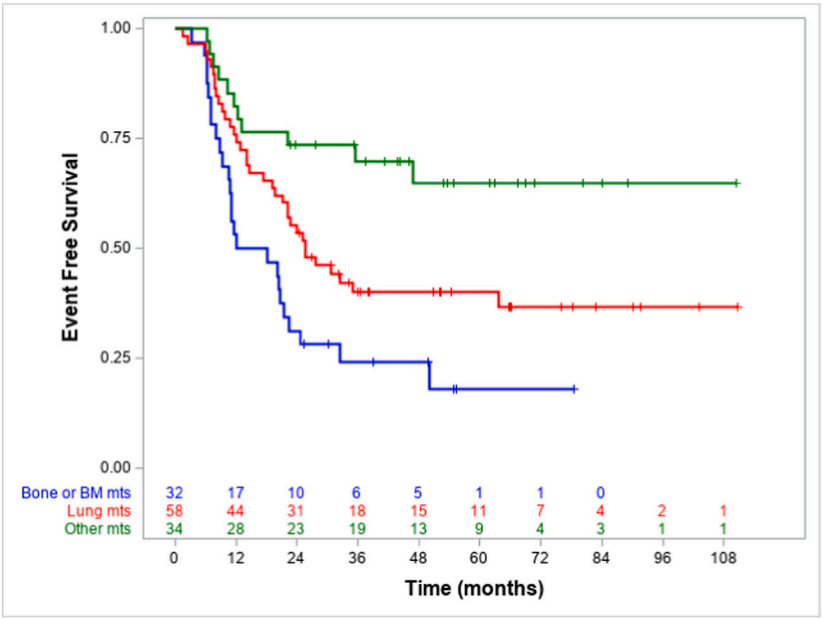
Fig. 1. (a) Event free survival by lung involvement. (b) Overall survival by lung involvement.

vs no RT 33%, 95%CI 16–52%, p = 0.0435. OS: 73%, 95%CI 51–86% versus 58%, 95%CI 36–75%; p = 0.2048 (Fig. 3a, b). The same analysis applied to patients with lung-only and lung + other metastases, showed the difference in survival according to lung RT received/not received was not significant (3-year EFS 45 vs 37%, p = 0.28; 3-year OS 56 vs 53%, p = 0.74) (Supplementary Fig 2a, b).

4. Discussion

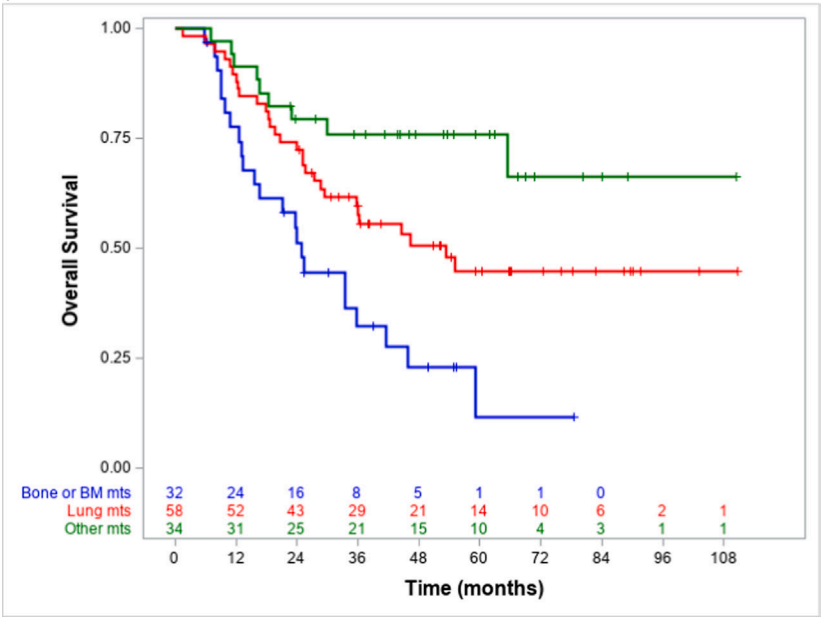
This large study of lung-only MTS RMS confirmed that 3-yr EFS and OS for patients with lung-only MTS RMS are better than for the whole metastatic population of MTS 2008 (3-yr EFS 40%, OS 60% versus EFS 35%, OS 48%) respectively [14]. The 40% 3-yr EFS for

a



	N	Failed	3-yr EFS (CI 95%)	p-value
Lung mts	58	35	40.2 (27.3-52.7)	0.0004
Bone or BM mts	32	25	24.1 (10.9-40.1)	
Other mts	34	11	69.9 (51.0-82.6)	

b



	N	Deaths	3-yr OS (CI 95%)	p-value
Lung mts	58	29	59.7 (45.8-71.1)	0.0002
Bone or BM mts	32	23	32.3 (16.2-49.6)	
Other mts	34	9	75.9 (57.4-87.2)	

Fig. 2. (a) Event Free Survival by metastatic involvement – one site of metastasis. (b) Overall Survival by metastatic involvement – one site of metastasis.

Table 2
Oberlin risk factors by patient group.

	Lung-only n = 59	Lung + other n = 68	Other n = 143	Total n = 270	%	p-value
0 factors	23	3	8	34	12.6	< **0.0001**
1 factor	30	14	37	81	30.0	
2 factors	6	16	51	73	27.0	
3 factors	–	24	34	58	21.5	
4 factors	–	11	13	24	8.9	

Table 3
Oberlin risk factors – one site of metastasis.

	Lung-only n = 59	Bone or BM n = 33	Other[a] n = 35	Total n = 127	%	p-value
0 factors	23	–	7	30	23.6	< 0.0001
1 factor	30	11	17	58	45.7	
2 factors	6	17	11	34	26.8	
3 factors	–	5	–	5	3.9	

[a] Patients with 1 metastatic site different from lung, bone, BM: 5 Peritoneum, 19 distant N, 1 liver, 4 pleura, 1 CNS, 1 subcutaneous, 4 other

lung-only RMS is similar to the 35% 4-year Failure Free Survival (FFS) reported in the Children's Oncology Group (COG) IRS IV study/pilot and 41% EFS in a report from the German Cooperative Weichteilsarkom Studiengruppe (CWS), but the OS of 60% reported here is higher compared to previous OS reports of 42% and 52%, respectively [12,17]. A very recent COG report including 55 lung-only MTS patients from 4 studies between 1999 and 2013 confirmed better outcomes in the lung-only MTS subgroup with 5 year FFS of 48% and OS of 64% [13].

A detailed study of 46 lung-only MTS RMS patients enrolled on the IRS IV study/pilot showed significantly better FFS and OS in lung-only patients than non-lung single site and ≥ 2 sites [12]. This is consistent with our findings of improved OS in the lung-only group compared to other groups. The only significant adverse risk factor identified was the number of metastatic sites and patients with ≤ 2 metastatic sites and favourable histology had 3-year OS of 47% [12]. Among MTS RMS patients enrolled on COG D9802, D9803, ARST0431 and ARST0431 studies, only single site metastatic disease (lung-only or other site) was significantly associated with improved outcome [13]. FOXO1 fusion data were not available for this analysis although earlier analysis of EFS by survival tree regression, including 220 MTS RMS patients from the D9802 and ARST0431 studies [13], implied that within the metastatic patient group, presence of a FOXO1 fusion is the most important adverse prognostic factor [18]. Fusion gene data were not consistently available in MTS 2008.

In the ARST0431 study, patients with MTS RMS were treated with a dose-intense multiagent regimen and irradiation recommended to primary and metastatic sites (with or without surgery) [8]. Those with 0–1 Oberlin risk factors had a 3-yr EFS of 69% comparing favourably to the 44% 3-yr EFS for the same group in Oberlin's study [11]. However, none of the COG analyses have undertaken detailed analysis of lung-only MTS by Oberlin risk factors.

In our analysis outcomes by Oberlin risk factors, patients with lung-only metastases in MTS 2008 had significantly fewer Oberlin risk factors than patients with lung + other or other sites and fewer risk factors than patients with another single site metastasis. Outcomes did not differ between lung-only and other patients when adjusted for the number of Oberlin risk factors. Other single metastatic site had better outcomes than lung-only or bone/bone marrow as a single metastatic site. These results suggest the main reason for better OS in lung-only MTS RMS patients is the association with fewer Oberlin risk factors. Whether EFS would reach significance with a larger data set remains unknown.

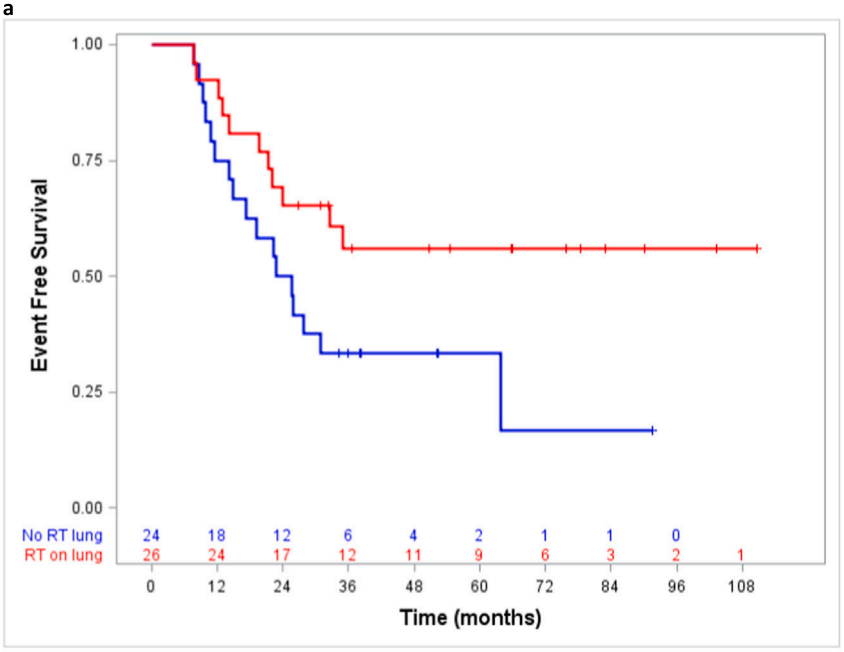
A previous CWS study of 53 patients with embryonal lung-only MTS RMS suggested benefit of lung RT on OS compared to surgical resection of metastases or no local therapy [17]. In the IRS IV and pilot studies, 30/46 (65%) lung-only MTS RMS patients received pulmonary RT and 4-year FFS and OS were significantly higher for patients who received lung RT compared to those who did not (OS 47 v 31%, p = 0.039; FFS 48 v 12%, p = 0.011, respectively) [12]. By contrast, the recent COG analysis showed no benefit of RT on survival outcomes for 28/54 (51%) receiving lung RT, but the analysis was not adjusted for difference between protocols in the timing of RT nor was a Landmark analysis done [13]. Despite protocol recommendations in MTS 2008, lung RT was given to only 26/57 (46%) of lung-only patients.

In the BERNIE [9], ARST0431 [8] and MTS 2008 [14] studies, 75%, 77% and 82% of MTS RMS patients, respectively, received RT to primary and/or metastatic sites. A retrospective analysis of patients in the BERNIE study suggested that delivery of RT to all (radical RT; OS 84%) or some (partial RT; OS 54%) disease sites was associated with improved outcome compared to no RT (OS 23%; Hazard Ratio 0.249, p = 0.00025) [16]. Similarly, in a recent single institution series of 80 patients with MTS RMS, 5-year OS was 76.0% for patients given radical RT, and 10.7% for those given partial RT or none, with OS correlating significantly with RT category in multivariable analysis [19]. Consistent with this, aggressive local treatment (surgery/RT) to the primary site was associated with improved outcomes in a retrospective French analysis of MTS RMS [20].

Omission of RT may occur for many reasons including young age, disease extent, early disease progression and investigator decision. Of interest, current CWS protocols do not recommend whole lung RT in patients with MTS RMS. Although the role of lung RT was not a predefined study question and the risk of bias exists, the significantly improved EFS in patients with lung-only MTS RMS receiving whole lung RT supports a role for lung RT in such patients [12]. Stereotactic radiotherapy is now an option for patients with oligometastatic disease [21,22] with excellent local control rates in sarcoma [23,24], better than achieved by surgery [24]. This approach allows delivery of doses substantially above the 15 Gy standard for whole lung RT and might be used with/without whole lung RT.

In conclusion, better OS in lung-only MTS RMS is associated with fewer Oberlin risk factors. A larger pooled analysis may clarify whether EFS as well as OS is improved in lung-only MTS RMS. Since outcomes in MTS RMS remain suboptimal, lung-only MTS RMS patients continue to be treated as other MTS patients within the current EpSSG Frontline and Relapse Rhabdomyosarcoma Study (FaR-RMS: NCT04625907), with lung RT recommended.

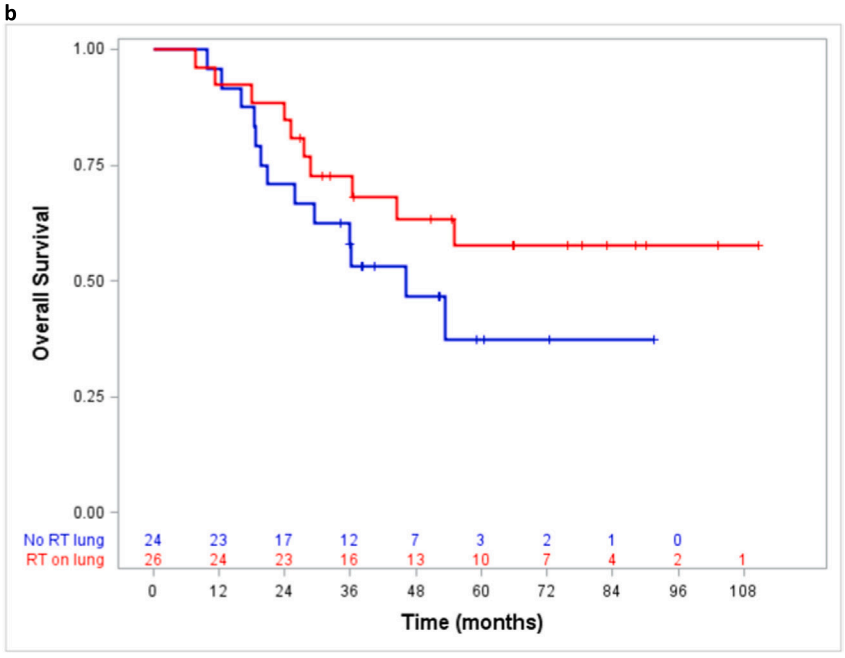
a



	N	Failed	3-yr EFS (CI 95%)	p-value
RT to Lung mts				0.0435
Yes	26	11	56.0 (34.5-73.0)	
No*	24	17	33.3 (15.9-51.9)	

*This group includes patients who received RT on sites other than lungs and patients who were not irradiated.
6 Patients with an event before DAY221 and 3 patients with missing data on radiotherapy treatment were excluded.

b



	N	Deaths	3-yr OS (CI 95%)	p-value
RT to Lung mts				0.2048
Yes	26	10	72.7 (51.1-86.0)	
No*	24	13	58.0(36.0-74.8)	

*This group includes patients who received RT on sites other than lungs and patients who were not irradiated.
6 Patients with an event before DAY221 and 3 patients with missing data on radiotherapy treatment were excluded.

Fig. 3. (a) Event Free Survival by RT to lung metastases in patients with lung-only MTS RMS. Excluding pts with event before Day 221. (b) Overall Survival by RT to lung metastases in patients with lung-only MTS RMS. Excluding patients with event before Day 221.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Previous presentation

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2023.100018.

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