

Supplemental Table 1. Risk grouping stratification and therapy

	Risk Group	Subgroup	Pathology	IRS Group	Site	Node Stage	Size & Age	Chemotherapy	Delayed surgery	RT
RMS 2005 study	Low	A	Favourable	I	Any	N0	Favourable	8 VA	Not necessary	No
	Standard	B	Favourable	I	Any	N0	Unfavourable	4 IVA + 5 VA	Not necessary	No
		C	Favourable	II, III	Favourable	N0	Any	9 IVA or 5 IVA + 4 VA if RT	Yes, if not mutilating	Optional
		D	Favourable	II, III	Unfavourable	N0	Favourable	9 IVA	Yes, if not mutilating	Yes
	High	E	Favourable	II, III	Unfavourable	N0	Unfavourable	9 IVA vs 4 IVADo + 5 IVA ± 6 VNL/CPM	Yes	Yes
		F	Favourable	II, III	Any	N1	Any			
		G	Unfavourable	I, II, III	Any	N0	Any			
	Very High	H	Unfavourable	II, III	Any	N1	Any	4 IVADo + 5 IVA + 6 VNL/CPM	Yes	Yes
MTS 2008 study	Metastatic patients		Any	IV	Any	Any	Any	4 IVADo + 5 IVA + 12 VNL/CPM	Yes	Yes

- **Pathology (histology):**

Favourable= all embryonal, spindle cells, botryoid RMS

Unfavourable= all alveolar RMS (including the solid-alveolar variant)

- **IRS Group=Post-surgical stage** (according to the IRS grouping, see appendix A.2):

Group I= primary complete resection (R0);

Group II= microscopic residual (R1) or primary complete resection but N1;

Group III= macroscopic residual (R2);

- **Site:**

Favourable= orbit, GU non bladder prostate (i.e. paratesticular and vagina/uterus) and non PM Head & neck

Unfavourable= all other sites (parameningeal, extremities, GU bladder-prostate and “other site”)

- **Node stage** (According to the TNM classification, see appendix A1 and A.5):

N0= no clinical or pathological node involvement

N1= clinical or pathological nodal involvement

- **Size & Age:**

Favourable= Tumour size (maximum dimension) ≤ 5 cm **and** Age <10 years

Unfavourable= all others (i.e. Size >5 cm **or** Age ≥ 10 years)

Chemotherapy:

VA = Vincristine 1.5 mg/m² (maximum dose 2 mg); plus Actinomycin D (maximum dose 2 mg)

IVA = Ifosfamide 3 g/m² given as a 3 h intravenous infusion with mesna (3 g/m²) and hydration on days 1 and 2, plus Vincristine 1.5 mg/m² (maximum dose 2 mg), weekly during the first 7 weeks, then only on day 1 of each cycle; plus Actinomycin D (maximum dose 2 mg) on day 1

IVADo = IVA plus doxorubicin 30 mg/m² on days 1 and 2 in the initial four cycles of chemotherapy

VNL-CPM = intravenous vinorelbine 25 mg/m² on days 1, 8, and 15 and oral cyclophosphamide 25 mg/m² per day given continuously for 24 weeks

Supplemental Table 2. Univariable analysis for the whole series of patients

	N	Events	5-yr EFS (95%CI)	p-value	Deaths	5-yr OS (95%CI)	p-value
All patients	1977	679	65.9 (63.7-67.9)	---	496	75.1 (73.1-77.1)	---
Gender							
Female	791	279	64.7 (61.2-68.0)	0.50	195	75.3 (71.9-78.3)	0.81
Male	1186	400	66.6 (63.8-69.3)		301	75.0 (72.4-77.5)	
Age at diagnosis							
<10 years	1422	449	68.6 (66.1-71.0)	<0.0001	303	79.5 (77.2-81.6)	<0.0001
≥10 years	555	230	58.7 (54.4-62.8)		193	63.9 (59.5-67.9)	
Age at diagnosis							
<15 years	1720	556	67.8 (65.5-70.0)	<0.0001	389	77.9 (75.8-79.8)	<0.0001
≥15 years	257	123	52.6 (46.3-58.6)		107	57.1 (50.4-63.1)	
Histology^a							
Favourable RMS	1407	393	72.2 (69.7-74.5)	<0.0001	260	82.0 (79.9-84.0)	<0.0001
Unfavourable RMS	570	286	50.2 (45.9-54.3)		236	58.2 (53.8-62.3)	
Tumour primary site^b							
Favourable site	709	155	78.0 (74.7-81.0)	<0.0001	73	89.7 (87.1-91.8)	<0.0001
Unfavourable site	1268	524	59.1 (56.3-61.8)		423	67.1 (64.3-69.7)	
Stage of disease							
Localised patients	1719	510	70.7 (68.4-72.8)	<0.0001	344	80.5 (78.5-82.4)	<0.0001
Metastatic patients	258	169	33.3 (27.4-39.3)		152	37.4 (30.8-44.0)	
IRS Group							
IRS I	210	24	88.6 (83.3-92.3)	<0.0001	12	94.4 (89.8-97.0)	<0.0001
IRS II	213	39	82.1 (76.1-86.8)		17	92.7 (87.9-95.6)	
IRS III	1296	447	65.9 (63.2-68.5)		315	76.3 (73.8-78.6)	
IRS IV	258	169	33.3 (27.4-39.3)		152	37.4 (30.8-44.0)	
T-invasiveness^c							
T1	1020	258	74.8 (71.9-77.4)	<0.0001	149	85.0 (82.5-87.2)	<0.0001
T2	939	413	56.4 (53.1-59.5)		341	64.6 (61.3-67.7)	
Tumor size^d							
≤5 cm	882	231	73.9 (70.8-76.7)	<0.0001	134	85.0 (82.3-87.3)	<0.0001
>5 cm	1068	432	59.9 (56.9-62.8)		351	67.5 (64.4-70.3)	
Loco-reg N^e							
N0	1515	439	71.4 (69.1-73.7)	<0.0001	278	82.3 (80.2-84.2)	<0.0001
N1	448	232	47.7 (42.9-52.3)		212	51.4 (46.4-56.2)	

^a18 T0/Tx patient excluded; ^b27 size x patients excluded; ^c14 Nx patient excluded

^a favourable RMS: embryonal RMS, botryoid RMS, spindle cell RMS;
unfavourable RMS: alveolar RMS, mixed embryonal/alveolar RMS, solid alveolar RMS, not-otherwise-specified RMS;

^b favourable site: orbit, HNnoPM, GUnoBP
unfavourable site: HNPM, GUBP, extremities, other sites, unknown

Legend:

RMS - rhabdomyosarcoma

IRS - Intergroup Rhabdomyosarcoma Study grouping

HNnoPM – head & neck, no parameningeal

HNPM - head & neck, parameningeal

GUBP – genito-urinary, bladder & prostate

GUnoBP - genito-urinary, no bladder & prostate

Supplemental Table 3. Univariable analysis for the whole series of patients, with hazard ratios

	N	Events	HR for EFS (95%CI)	p-value	Deaths	HR for OS (95%CI)	p-value
Gender							
Female	791	279	1	0.49	195	1	0.81
Male	1186	400	0.948 (0.814-1.105)		301	1.022 (0.854-1.224)	
Age at diagnosis							
<10 years	1422	449	1	<0.0001	303	1	<0.0001
≥10 years	555	230	1.451 (1.238-1.701)		193	1.831 (1.528-2.193)	
Age at diagnosis							
<15 years	1720	556	1	<0.0001	289	1	<0.0001
≥15 years	257	123	1.684 (1.385-2.047)		107	2.090 (1.687-2.589)	
Histology^a							
Favourable RMS	1407	393	1	<0.0001	260	1	<0.0001
Unfavourable RMS	570	286	2.095 (1.798-2.440)		236	2.548 (2.136-3.039)	
Tumour primary site							
Favourable site	709	155	1	<0.0001	73	1	<0.0001
Unfavourable site	1268	524	2.191 (1.831-2.621)		423	3.741 (2.918-4.796)	
Stage of disease							
Localised patients	1719	510	1	<0.0001	344	1	<0.0001
Metastatic patients	258	169	3.285 (2.757-3.914)		152	4.675 (3.852-5.674)	
IRS Group							
IRS I	210	24	1	<0.0001	12	1	<0.0001
IRS II	213	39	1.643 (0.988-2.733)		17	1.419 (0.678-2.972)	
IRS III	1296	447	3.507 (2.325-5.288)		315	4.774 (2.682-8.497)	
IRS IV	258	169	9.587 (6.246-14.713)		152	17.936 (9.954-32.322)	
T-invasiveness^b							
T1	1020	258	1	<0.0001	149	1	<0.0001
T2	939	413	1.986 (1.700-2.321)		341	2.836 (2.339-3.438)	
Tumor size^c							
≤5 cm	882	231	1	<0.0001	134	1	<0.0001
>5 cm	1068	432	1.709 (1.457-2.005)		351	2.387 (1.956-2.913)	
Loco-reg N[*]							
N0	1515	439	1	<0.0001	278	1	<0.0001
N1	448	232	2.188 (1.866-2.567)		212	3.300 (2.758-3.948)	

^a18 T0/Tx patient excluded; ^b27 size x patients excluded; ^{*}14 Nx patient excluded

^a favourable RMS: embryonal RMS, botryoid RMS, spindle cell RMS;
unfavourable RMS: alveolar RMS, mixed embryonal/alveolar RMS, solid alveolar RMS, not-otherwise-specified RMS;

^b favourable site: orbit, HNnoPM, GUnoBP
unfavourable site: HNPM, GUBP, extremities, other sites, unknown

Legend:

RMS - rhabdomyosarcoma

IRS - Intergroup Rhabdomyosarcoma Study grouping

HNnoPM – head & neck, no parameningeal

HNPM - head & neck, parameningeal

GUBP – genito-urinary, bladder & prostate

GUnoBP - genito-urinary, no bladder & prostate

Supplemental Table 4. Univariable analysis for localised and metastatic patients**Localised patients**

	N	Events	5-yr EFS (95%CI)	p-value	Deaths	5-yr OS (95%CI)	p-value
All patients	1719	510	70.7 (68.4-72.8)	---	344	80.5 (78.5-82.4)	---
Gender							
Female	678	208	69.5 (65.7-72.8)	0.44	133	80.7 (77.3-83.6)	0.80
Male	1041	302	71.5 (68.6-74.2)		211	80.4 (77.7-82.7)	
Age at diagnosis							
<10 years	1285	375	71.1 (68.5-73.6)	0.34	240	82.3 (80.0-84.4)	0.0097
≥10 years	434	135	69.4 (64.7-73.6)		104	75.0 (70.4-79.0)	
Age at diagnosis							
<15 years	1523	437	71.6 (69.2-73.9)	0.013	286	81.9 (79.8-83.8)	0.0004
≥15 years	196	73	63.6 (56.3-69.9)		58	69.7 (62.4-75.9)	
Histology^a							
Favourable RMS	1297	336	74.3 (71.8-76.6)	<0.0001	209	84.6 (82.4-86.5)	<0.0001
Unfavourable RMS	422	174	59.7 (54.7-64.2)		135	68.3 (63.4-72.7)	
Tumour primary site							
Favourable site	680	135	80.1 (76.8-82.9)	<0.0001	56	91.9 (89.4-93.8)	<0.0001
Unfavourable site	1039	375	64.6 (61.6-67.5)		288	73.2 (70.3-75.9)	
IRS Group							
IRS I	210	24	88.6 (83.3-92.3)	<0.0001	12	94.4 (89.8-97.0)	<0.0001
IRS II	213	39	82.1 (76.1-86.8)		17	92.7 (87.9-95.6)	
IRS III	1296	447	65.9 (63.2-68.5)		315	76.3 (73.8-78.6)	
T-invasiveness^b							
T1	953	219	77.2 (74.3-79.8)	<0.0001	115	87.8 (85.4-89.8)	<0.0001
T2	754	287	62.6 (59.0-66.0)		227	71.3 (67.8-74.4)	
Tumor size^c							
≤5 cm	828	196	76.5 (73.4-79.3)	<0.0001	101	88.2 (85.7-90.3)	<0.0001
>5 cm	874	306	65.6 (62.3-68.7)		239	73.4 (70.3-76.3)	
Loco-reg N^d							
N0	1419	382	73.5 (71.1-75.8)	<0.0001	229	84.7 (82.6-86.5)	<0.0001
N1	291	124	57.3 (51.3-62.8)		113	60.6 (54.4-66.1)	

^a12 T0/Tx patient excluded; ^b17 size x patients excluded; ^c9 Nx patient excluded

Metastatic patients

	N	Events	5-yr EFS (95%CI)	p-value	Deaths	5-yr OS (95%CI)	p-value
All patients	258	169	33.3 (27.4-39.3)	---	152	37.4 (30.8-44.0)	---
Gender							
Female	113	71	35.7 (26.4-45.0)	0.23	62	38.7 (27.9-49.4)	0.25
Male	145	98	31.5 (23.9-39.3)		90	35.8 (27.4-44.2)	
Age at diagnosis							
<10 years	137	74	44.5 (35.6-53.1)	<0.0001	63	51.1 (41.4-60.0)	<0.0001
≥10 years	121	95	20.6 (13.8-28.4)		89	22.6 (14.9-31.4)	
Age at diagnosis							
<15 years	197	119	38.1 (31.0-45.2)	0.0002	103	44.7 (36.8-52.3)	<0.0001
≥15 years	61	50	17.7 (9.3-28.2)		49	15.8 (7.3-27.1)	
Histology^a							
Favourable RMS	110	57	47.5 (37.6-56.8)	0.0002	51	50.8 (40.2-60.5)	0.0008
Unfavourable RMS	148	112	22.8 (16.1-30.2)		101	27.6 (19.7-36.0)	
Tumour primary site							
Favourable site	29	20	31.0 (15.6-47.9)	0.62	17	40.3 (22.4-57.7)	0.99
Unfavourable site	229	149	33.5 (27.1-39.9)		135	37.0 (29.9-44.0)	
T-invasiveness^b							
T1	67	39	40.8 (28.8-52.5)	0.20	34	43.5 (29.7-56.5)	0.25
T2	185	126	30.8 (24.0-37.8)		114	35.6 (28.1-43.2)	
Tumor size[^]							
≤5 cm	54	35	34.4 (22.0-47.2)	0.89	33	32.3 (18.5-47.0)	0.43
>5 cm	194	126	34.3 (27.5-41.2)		112	38.9 (31.3-46.4)	
Loco-reg N*							
N0	96	57	40.5 (30.3-50.3)	0.051	49	45.1 (33.7-55.8)	0.016
N1	157	108	29.4 (22.2-37.0)		99	33.4 (25.2-41.7)	

[^]6 T0/Tx patient excluded; [^]10 size x patients excluded; *5 Nx patient excluded

^a favourable RMS: embryonal RMS, botryoid RMS, spindle cell RMS;
unfavourable RMS: alveolar RMS, mixed embryonal/alveolar RMS, solid alveolar RMS, not-otherwise-specified RMS;

^b favourable site: orbit, HNnoPM, GUnoBP
unfavourable site: HNPM, GUBP, extremities, other sites, unknown

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Supplemental Table 4. Multivariable analysis of survival

Event Free Survival (n=1925, events=653)*		Hazard Ratio (CI 95%)		p-value
Age at diagnosis	<15 years	1		0.0002
	≥15 years	1.484	1.203-1.831	
Stage of disease	Localised disease	1		<0.0001
	Metastatic disease	2.067	1.692-2.525	
T-invasiveness	T1	1		<0.0001
	T2	1.468	1.237-1.741	
Loco-regional node involvement	N0	1		0.0074
	N1	1.287	1.070-1.547	
Overall Survival (n=1925, deaths=479) **		Hazard Ratio (CI 95%)		p-value
Age at diagnosis	<15 years	1		<0.0001
	≥15 years	1.733	1.371-2.189	
Tumour primary site	Favourable	1		<0.0001
	Unfavourable	2.212	1.678-2.917	
Stage of disease	Localised disease	1		<0.0001
	Metastatic disease	2.330	1.869-2.906	
Loco-regional node involvement	N0	1		<0.0001
	N1	1.685	1.369-2.075	

* Multivariate analysis was performed for EFS including variables with $p < 0.25$ at univariable analysis: age at diagnosis (<15 vs ≥15 yrs), histology, tumour primary site, stage of disease, T-invasiveness, tumour size, and loco-regional nodes involvement. The hazard ratios assumption of non-proportionality was tested for all these variables including time-dependent covariates in the model. PH assumption was violated for histology and site, therefore a stratified Cox model was performed with age at diagnosis, stage of disease, tumour primary size, T-invasiveness and loco-regional nodes involvement.

** Multivariate analysis has been performed for OS including variables with $p < 0.25$ at univariable analysis: age at diagnosis (<15 vs ≥15 yrs), histology, tumour primary site, stage of disease, T-invasiveness, tumour size, and loco-regional nodes involvement. The hazard ratios assumption of non-proportionality was tested for all these variables including time-dependent covariates in the model. PH assumption was violated for histology, T-invasiveness and size, therefore a stratified Cox model was performed with age at diagnosis, tumour primary site, stage of disease and loco-regional nodes involvement.