Management of Low and Intermediate Risk Adult Rhabdomyosarcoma: A Pooled Survival Analysis of 553 Patients

Maha AT Elsebaie[1], Mohamed Amgad[†2], Ahmed Elkashash[†3], Ahmed Saber Elgebaly[4,5], Gehad Gamal El Ashal[3,5], Emad Shash[6], Zeinab Elsayed[*7]

1 Faculty of Medicine, Ain Shams University, Cairo, Egypt.

2 Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, USA.

3 Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt

4 Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

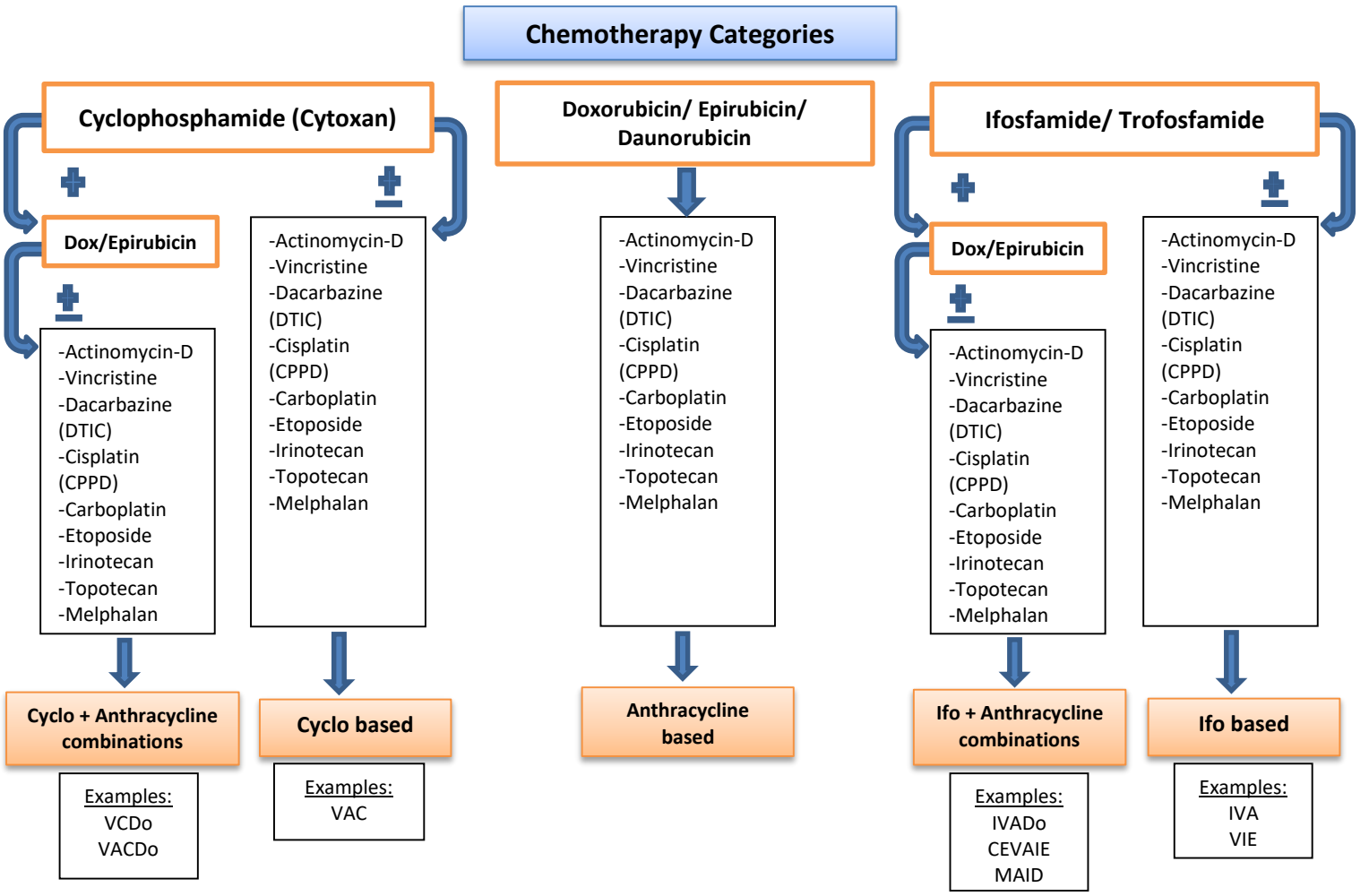
5 Medical Research Education and Practice Association (MREP)

6 Medical Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt.

7 Adult Sarcoma Division, Clinical Oncology Department, Ain Shams University Hospitals, Cairo, Egypt.

† Authors contributed equally

Supplementary 4.1: Categorization System for Different Chemotherapy Categories



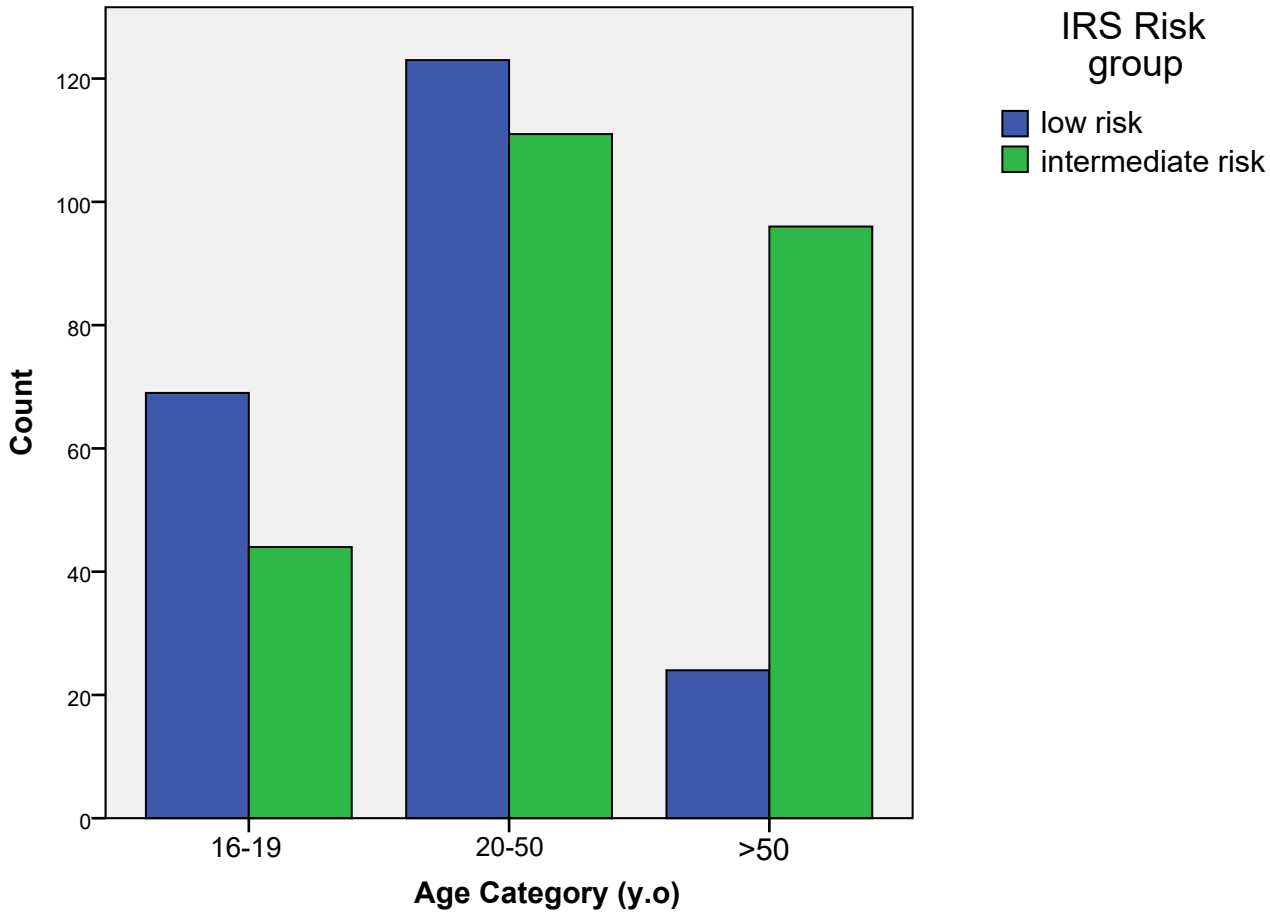
Others	No Dox or IFo or Cyclo Example: VA (Vincristine/ Actinomycin-D)
Cyclo+Dox+Ifo Combination	A combination containing all three drugs

VAC: Vincristine, Actinomycin-D, Cyclophosphamide.
VACDo: VAC + Doxorubicin
IVA: Ifosfamide, Vincristine, Actinomycin-D.
IVADo: IVA + Doxorubicin
VIE: Vincristine, Ifosfamide, Etoposide.
CEVAIE: carboplaifotin, etoposide, vincristine, Actinomycin-D, ifosfamide, epirubicin.
MAID: mesna, doxorubicin, ifosfamide, dacarbazine.

Supplementary 4.2: Quality assessment Criteria

Criteria for Assessment	High quality (pool data for survival-analysis)	Intermediate quality (Email principal author for missing data)	Low quality (excluded from the analysis)
Patient population clearly identified (*Adult > 16 y.o; primary, pathologically proven, non-metastatic RMS*)	Yes	Yes	Any (e.g. Excluded studies are those describing rhabdomyosarcoma as a teratomatous tumor or mixed tumor)
Minimal demographic and clinicopathological characteristics are clearly specified for individual patients? *Age, sex, subtype, stage, staging system, primary site*.	Yes	yes	Any
Treatment modality mentioned?	Yes	Yes	No
Types of chemotherapy mentioned?	Yes	yes	No
Types of chemotherapy specified for individual patients rather than for groups?	Yes	Any (Only if they mention that exact chemotherapy regimen were available for all patients	No
Timing of chemotherapy mentioned?	Yes	Any	No
Intervention data specified for individual patients rather than for groups?	Yes	Any	No
Follow up data available for individual patients?	Yes	Yes	No (e.g. recent cases)
Missing data of interest (other than the aforementioned data) *(e.g. tumor size, T status, Nodal status, timing and dose of radiotherapy)*	No	Any	Any
Objective? Did the study aim to compare the efficacy of different chemotherapy regimens/ treatment protocols/ treatment modalities on survival outcomes?	yes	yes	No (e.g. Clinicopathological, ultra-structural, immunophenotypic and genetic studies)

Supplementary 4.3: Distribution of the different age groups between low and intermediate risk patients



Supplementary 4.4: Pairwise comparisons of the effect different Chemotherapeutic regimens on PFS and OS

Chemotherapy Category	N.	5-y PFS	Cyclo based	Cyclo and Anthracycline based	Ifo based	Ifo and Anthracycline based	Anthracycline based	Cyclo and Ifo and Anthracyclin combination$^{\pi}$	Other/ Unknown
				***p*-value of Pairwise Comparisons (Gehan-Wilcoxon statistic)**					
Cyclo based	85	64%		0.198	0.645	0.826	0.091	0.227	0.05
Cyclo and Anthracycline based	78	74%	0.198		0.671	0.194	0.016	0.594	0.001
Ifo based	15	*	0.645	0.671		0.54	0.08	0.324	0.163
Ifo and Anthracycline based	52	63%	0.826	0.194	0.54		0.135	0.205	0.165
Anthracycline based	18	47%	**0.091**	**0.016**	0.08	0.135		**0.037**	0.554
Cyclo and Ifo and Anthracycline combination	14	80%	0.227	0.594	0.324	0.205	0.037		0.038
Other/Unknown	115	45%	0.05	0.001	0.163	0.165	0.554	0.038	

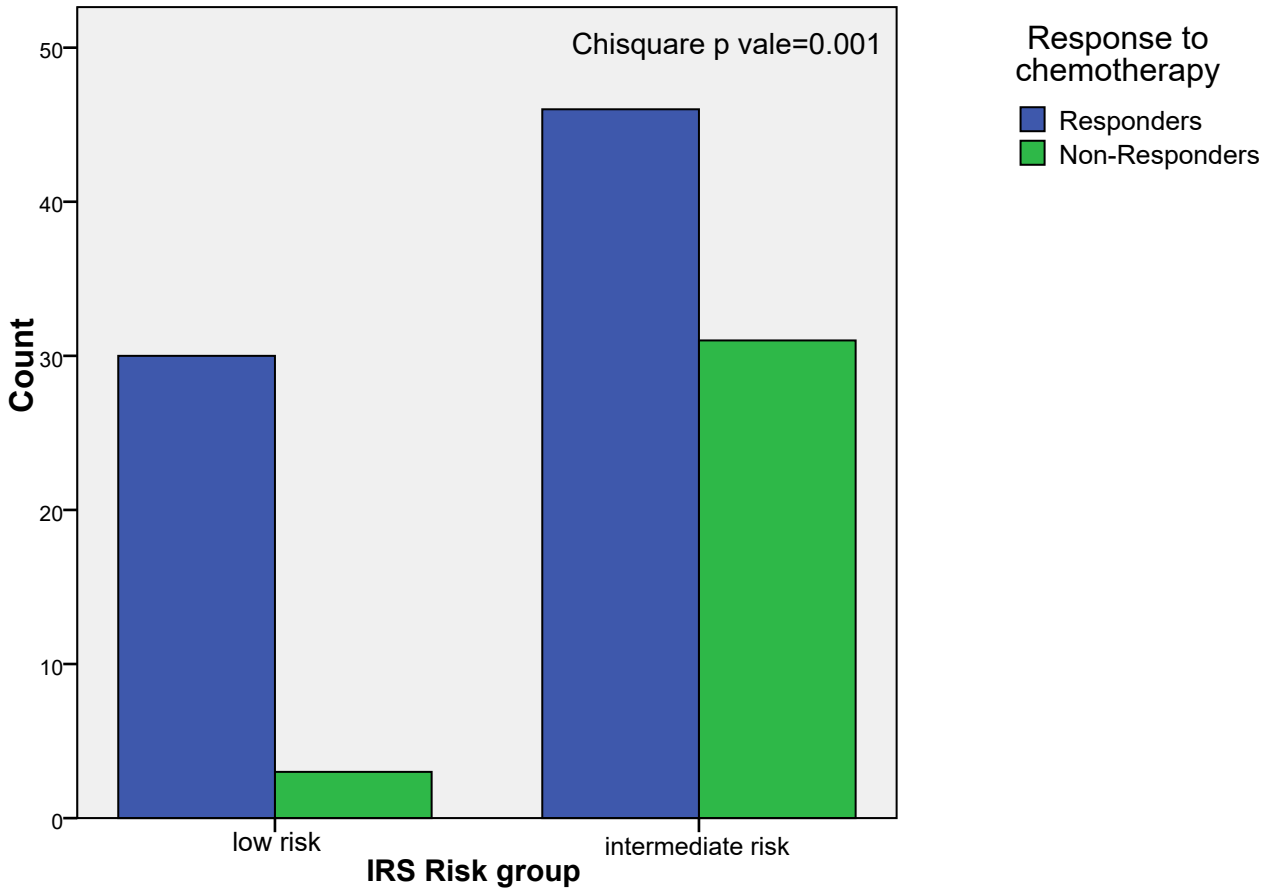
PFS: Progression-free survival; * No 5y-PFS available (maximum PFS months available for this group is 50 months).

$^{\pi}$ 14 patients received intensified chemotherapy consisting of cyclophosphamide/anthracycline/ifosfamide combination-based regimen, with excellent 5y-PFS of 80% (*p*=0.037)

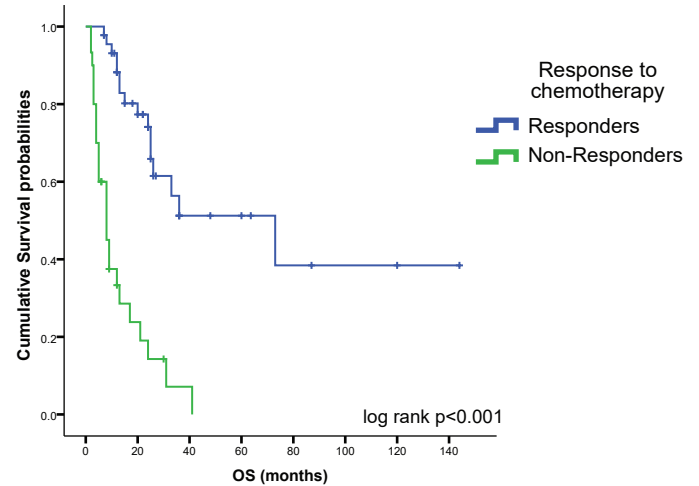
Cyclo: Cyclophosphamide; Ifo: Ifosfamide; Anthracycline: Doxorubicin/ Epirubicin/ Daunorubicin

Chemotherapy Category	N.	5-y OS	Cyclo based	Cyclo and Anthracycline based	Ifo based	Ifo and Anthracycline based	Anthracycline based	Cyclo and Ifo and Anthracycline combination	Other/Unknown
				***p*-value of Pairwise Comparisons (Gehan-Wilcoxon statistic)**					
Cyclo based	85	56%		0.014	0.689	0.349	0.022	0.363	0.159
Cyclo and Anthracycline based	78	78%	**0.014**		0.44	**0.003**	0.000	0.659	**0.000**
Ifo based	15	71%	0.689	0.44		0.381	0.087	0.563	0.295
Ifo and Anthracycline based	52	57%	0.349	0.003	0.381		0.232	0.217	0.847
Anthracycline based	18	36%	**0.022**	**0.000**	0.087	0.232		**0.039**	0.151
Cyclo and Ifo and Anthracycline combination	14	48%	0.363	0.659	0.563	0.217	0.039		0.12
Other/Unknown	115	42%	0.159	0.000	0.295	0.847	0.151	0.12	

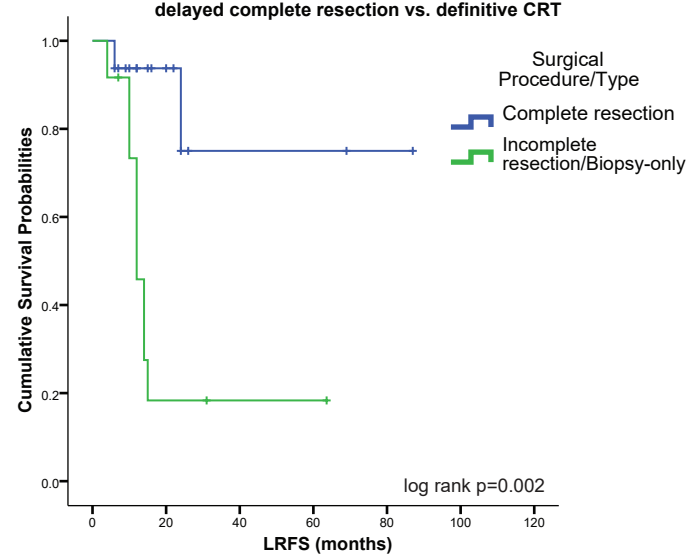
Supplementary 4.5: Distribution of the chemotherapy response between low and intermediate risk patients



Supplementary 4.6: OS outcomes of intermediate risk patients who showed response (CR/PR) vs. no response/disease progression (NR/PD)



Supplementary 4.7: Local control of PR/NR cohort treated with delayed complete resection vs. definitive CRT



Supplementary 4.8: Comprehensive Comparison of the largest retrospective analysis Performed on adult RMS patients as of September, 2016

Study	La Quaglia et al, 1994	Esnaola et al, 2001	Hawkins et al, 2001	Little et al, 2002	Ferrari et al, 2003	Simon et al, 2003	Sultan et al, 2009	Gerber et al, 2013	Van Gaal et al, 2012	Dumont et al, 2013	Kojima etal, 2012
Patient Source	Memorial Sloan-Kettering Cancer Center	Dana Farber Cancer Institute	Memorial Sloan-Kettering Cancer Center	M.D. Anderson Cancer Center	Milan, Italy	USA	SEER Database	Memorial Sloan-Kettering Cancer Center	Netherlands	MD Anderson Cancer Center	Japan
Population size	290	39	84	82	171	39	1071	138	169	239	36
Population type	Mixed (Target is 133)	Target patients analyzed separately	Mixed (47M0, 37M1) analysis	Target	Target patients analyzed separately	Mixed (33M0, 6M1) analysis	Target patients analyzed separately	Target patients analyzed separately	Only Emb and Alv	Target patients analyzed separately	Target patients analyzed separately
Non-metastatic adults	133	26	47	82	149	33	617	94	34 (51 adults, 17 metastatic)	163	22
5y-OS for non-metastatic patients		44%	N/A (Median DSS survival is 35 vs. 14)	44%	45.7%	N/A (35% for whole cohort)	47%	45%	40±13% (E, non-metastatic)	44.1% with 95% CI 0.362–0.516	55-60%* *Deducted from KM curve
Received Chemo		24	-	56	110	22	N/A	81		146	22
Type of Chemo		14 patients received **VAC** while 10 patients received doxorubicin-based or ifosfamide-containing regimens.		Vin and Cyclo with Act **(VAC)** or DOX **(VACA).**	**74 received a chemotherapy score of 1** → multidrug regimen consisting of cyclophosphamide or ifosfamide, with doxorubicin, epirubicin, and/or dactinomycin, with without vincristine (and with or without other drugs, such as dacarbazine, cisplatin, carboplatin, and etoposide); and lasted for 8 cycles or more. **They assigned scores of 0.4, 0.5, and 0.6** to chemotherapy regimens lasting 2, 4,	The most commonly employed agents were VAC in seven, actinomycin-D alone in four and VA in three patients.		OS rates were significantly better for adults patients treated according to a prospective RMS protocol compared to patients treated off protocol. In comparing the two patient groups, they found that protocol patients were more likely to receive cyclophosphamide, doxorubicin, and vincristine compared to non-protocol patients		**39% received Doxorubicin-based (No ifo/cyclo),** 3% had Ifo-based, 12% had Ifo/Dox based regimens, 20% Any Act-D (No Dox, Ifo), 11% Unknown. "Any actinomycin D, No doxorubicin/ifosfamide" were significantly associated with longer RFS but lost significance on multivariate level.	VAC or VAC-like chemotherapy. according to IRS-IV (D9803) protocols. The VAC-like regimen includes the following regimens: vincristine, d-actinomycin, and either ifosfamide, etoposide, or doxorubicin.

					or 6 cycles, and a score of 0.5 to chemotherapy regimens that did not include cyclophosphamide or ifosfamide (i.e., doxorubicin-based).			(71% vs 20%, p<0.0001)			
5-y OS for non-metastatic patients who received chemotherapy		5-y OS rate 44%		10-y OS rate 47%	5-y OS 49.9%: **Score 1** 5y-OS 11.5% for **score 0.4-0.5** Five-year OS 45.7% for entire cohort of non-metastatic patients.			3-y, 4-y and 5-y OS (71%, 61%, and 54%, respectively). for non-metastatic patients treated on protocol. On MVA, risk group (intermediate vs low, HR 2.78, 95% CI 1.40-5.53, PZ.004) and protocol participation were independent prognosticators.	5-year OS 49.2±15.4%	Median OS of 3.8 years (95% CI 2.8–7.6). The 2-year OS was 0.660 with 95% CI 0.582–0.727, and the 5-year OS was 0.441 with 95% CI 0.362–0.516.	
5-yPFS/ EFS/DMFS for patients who received chemotherapy				10y-DMFS 59%	5y-DMFS 64.1% **Score 1** 5y-DMFS 27.8% for **score 0.4-0.5** Five-year DMFS 56.2% for entire cohort of non-metastatic patients. Five-year EFS 32.9% for entire cohort of non-metastatic patients.			DM rate at 5 years was 42%. The failure rates at 5 years for patients with nonmetastatic disease were 34% for local failure and 42% for distant failure.		The median RFS was 1.9 years (95% CI 1.3–2.8 years). the 5-year RFS rate was 0.362 (95% CI 0.288–0.436).	Median PFS of localized children and adults was as follows: 166.9 versus 22.4 months (p = 0.005). and metastatic disease, 13.3 versus 13.3 months (p = 0.949),
Age (y)											
Univariate	Significant OS	Not significant OS (<26y; >26y)	Significant: Age (<20, >20) on DSS, DMFS and LRFS.	Not significant (<28; >28) on OS, DFS, LRFS, DMFS	Not significant (19-30; 31-60; >60) on OS, FFS (p=0.9393)	Not significant	Significant on OS, DSS	Significant (continuous variable) on OS (p=0.02)	Significant (<16, >16) on DSS, PFS	Significant (<20, 20-50, >50) OS, RFS	Significant (<21 vs. >21) on PFS

Multivariate	Significant OS (p=0.0001)	Not significant OS	Significant: Age (<20, >20) on DSS, DMFS and LRFS.	Not significant on OS, DFS, LRFS, DMFS	Not tested	Not significant	Significant on OS, DSS	Not significant OS	The only significant factor for PFS. Significant on DSS	Significant OS, RFS	Significant on PFS. Not significant on OS
Primary Tumor site (Favorable vs. Unfavorable)											
Univariate	Not significant OS	Not significant 5y OS 42% vs.14% vs. 39%	Not significant	Significant on LRFS PM vs. all other sites 50% versus 83%	Not significant on OS, EFS (p=0.6809)	Not significant	Significant on OS, DSS	Significant on OS, DMFS	Significant on DSS, PFS	Significant (GU) OS, PFS	Not reported
Mulivariate	Not significant OS	Not significant	Not significant on DSS or DMFS	The only significant predictor factor on LRFS (PM site, p=0.003)	Not tested	Significant OS	Not significant	Significant on DMFS only	Significant on DSS, PFS	Not significant on PFS, OS	Not reported
Histological subtype (E vs. non-E)											
Univariate	Significant OS (p=0.0446)	Not significant 5y OS 43% vs. 29% vs. 26%	Not significant	*Significant 10y OS 27% vs. 44%, 10-year DMFS 32% vs. 58%	Significant 5y-OS 58.% vs. 30%; Significant EFS	Not significant	PRMS/ARMS significant OS, DSS	Significant DMFS, LRFS, OS	Not tested	Not reported	Not reported
Mulivariate	Significant only if Pleomorphic RMS was involved	Not significant OS	Not significant on DSS or DMFS	Not significant	Not tested	Significant OS (0.009), PFS	Significant OS, DSS only if Pleomorphic RMS was involved	Significant on DMFS and the only significant predictor of LRFS	Not tested	Not reported	Not reported

Tumor invasiveness (T1 vs. T2)											
Univariate	Significant OS	Significant 5y OS (p<0.0001)	Significant DSS (Local vs. distant)	Not reported	Significant 5y-OS 77% vs. 30.9% and EFS	Not significant	Significant (regional vs. Localized) on OS, DSS	Not reported	Not tested	Not reported	Not reported
Mulivariate	Significant OS (p<0.0001)	Not significant	Significant DSS	Not reported	Not tested	Significant OS (p=0.034), PFS	Significant on OS, DSS	Not reported	Not tested	Not reported	Not reported
Tumor size (<5 vs. >5 cm)											
Univariate	Not reported	Significant 5y OS 60% vs. 11%	5y-DSS 52% vs. 22%	Signifiacnt OS, DFS, DMFS 10y OS 49% vs. 35%	Significant 5y-OS 75% vs. 30.4% and EFS	Not reported	Not reported	Not reported	Not tested	Not significant OS, RFS	Not reported
Mulivariate	Not reported	Not significant	Significant on MVA of DSS (p<0.03) BUT lost significance in MVA of LRFS or DMFS.	The only significant predictor on DFS, DMFS.	Not tested	Not reported	Not reported	Not reported	Not tested	Not significant OS, RFS	Not reported