

UC San Diego Health

Case Conference: Retroperitoneal Sarcoma



AJCC 7th edition staging

- **T1 - less than or equal to 5cm (T1a superficial, T1b deep);**
- **T2 - greater than 5 cm (T2a superficial, T2b deep);**
- **Retroperitoneal location is always deep**

- **N1 - regional lymph node metastasis;**
- **M1 - distant metastasis**
- **AJCC 2002 Staging System**

- **Stage I - All low grade, N0, M0**
- **Stage II - T1a/b-T2a, N0, high grade**
- **Stage III - T2b, N0, high grade**
- **Stage IV - N1 or M1, any grade**
- **Dutch/Memorial Sloan Kettering Classification System**

- **Stage I - low grade, complete resection, no mets**
- **Stage II - high grade, complete resection, no mets**
- **Stage III - any grade, incomplete resection, no mets**
- **Stage IV - distant mets**

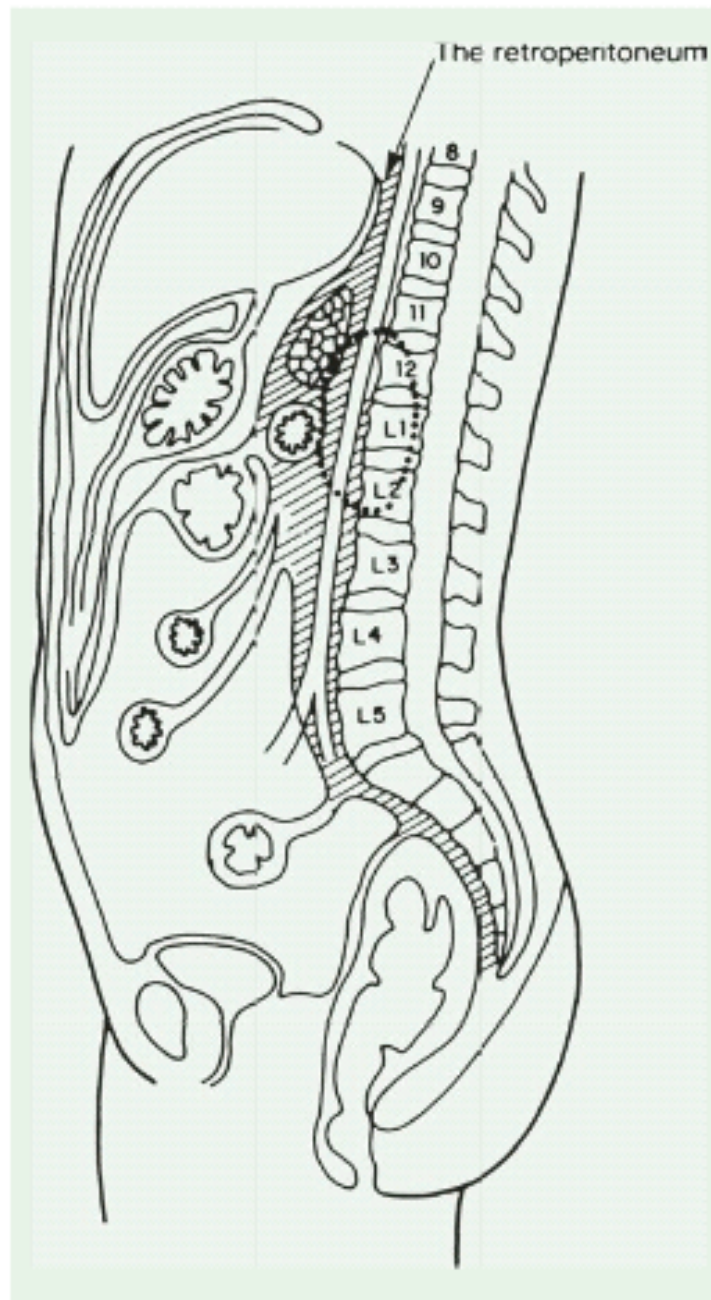


FIGURE 73.1. Sagittal view of trunk, showing the retroperitoneal space (shaded area). The kidney is outlined by dots. (From Wasserman TH, Tepper JE. Retroperitoneum. In: Perez CA, Brady LW, eds. *Principles and practice of radiation oncology*, 3rd ed. Philadelphia: Lippincott-Raven; 1997:1943–1956, with permission.)

Epidemiology

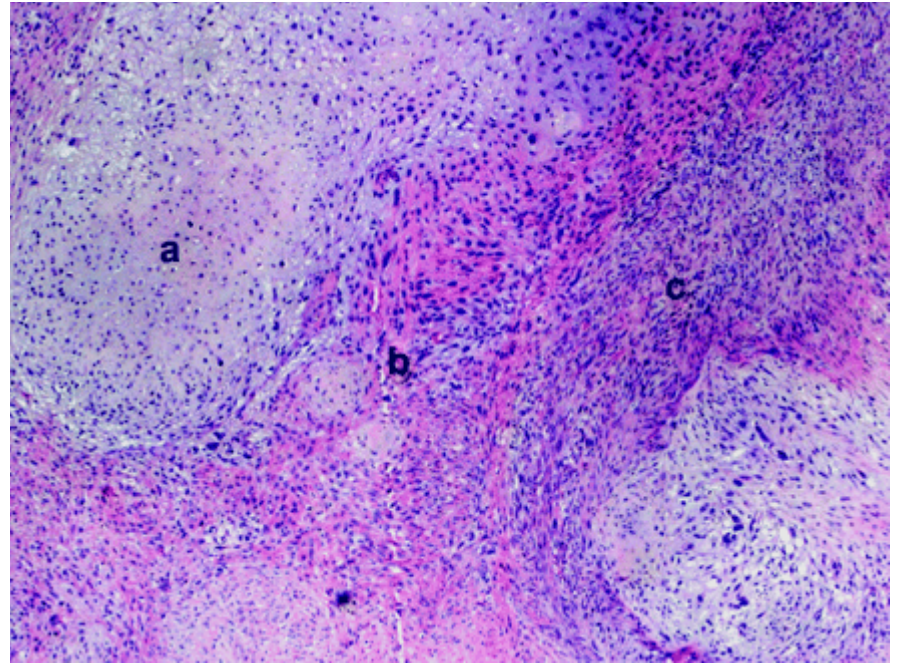
- 10-15% of sarcomas are retroperitoneal
- US incidence of RP sarcoma is about 1,000 cases per year
- Median size at diagnosis is 15cm
- 5% likelihood of nodal involvement at diagnosis
- GTR is feasible in 50-67%

- R0 – complete resection, microscopically negative margins
- R1 – microscopically positive margin
- R2 – gross residual disease

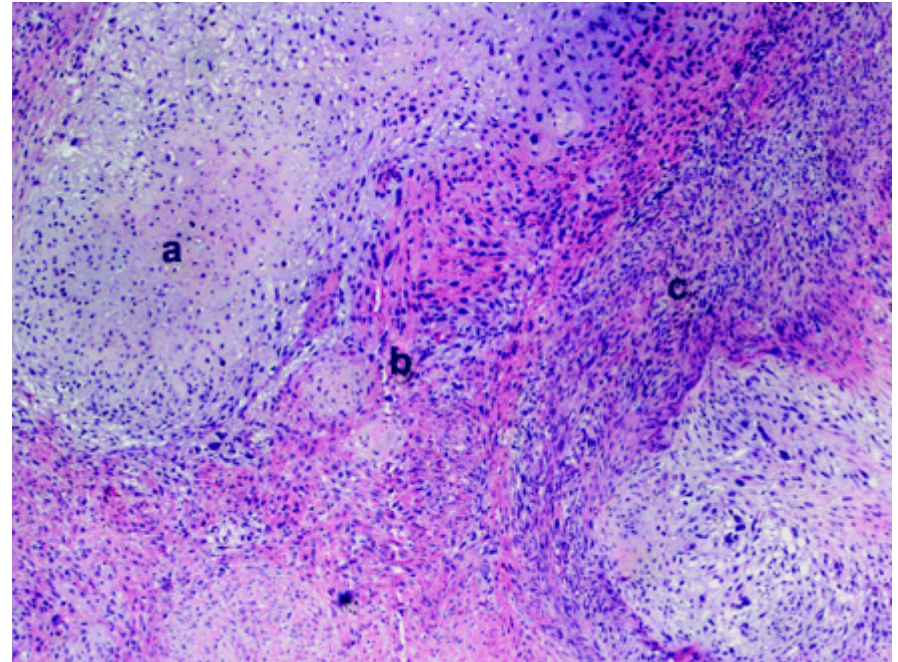
- Even after R0 resection the 5yr LR rate is 33-77% and 5yr OS is 35-63%, with most patients dying of local disease

MPNST

- MPNST is 5-10% of STS
- Prior RT is a risk factor
- NF1 is a risk factor – 4-5% of pts with NF1 will develop MPNST
- On Pathology:
 - Loss of NF1 (neurofibromin) gene, high RAS activity
 - Loss of p27-Kip1, p53, or p16



Tritons



MPNSTs with rhabdomyoblastic differentiation are called “triton tumors”.



Trials and Recommendations

Recommendations

- Surgery is the mainstay of treatment:
 - maximal safe resection en bloc with adherent structures.
 - Lymphadenectomy not indicated if uninvolved
 - Palliative debulking may be performed
- Various RT options exist:
 - Pre-op RT to 45-50Gy (GTV -> CTV = 1.5cm), followed by surgery 3-8wks later
 - Post-op RT to $\geq 54-60$ Gy
 - IORT boost or brachytherapy boost of 10-20 Gy may be considered

Advantages of pre-op RT

- Better target delineation
- Smaller fields
- Less normal tissue treated
- Hypothetical decrease in risk of wound or peritoneal seeding
- Radiobiologic advantage of treated vascularized/oxygenated tumor

Post-Op RT

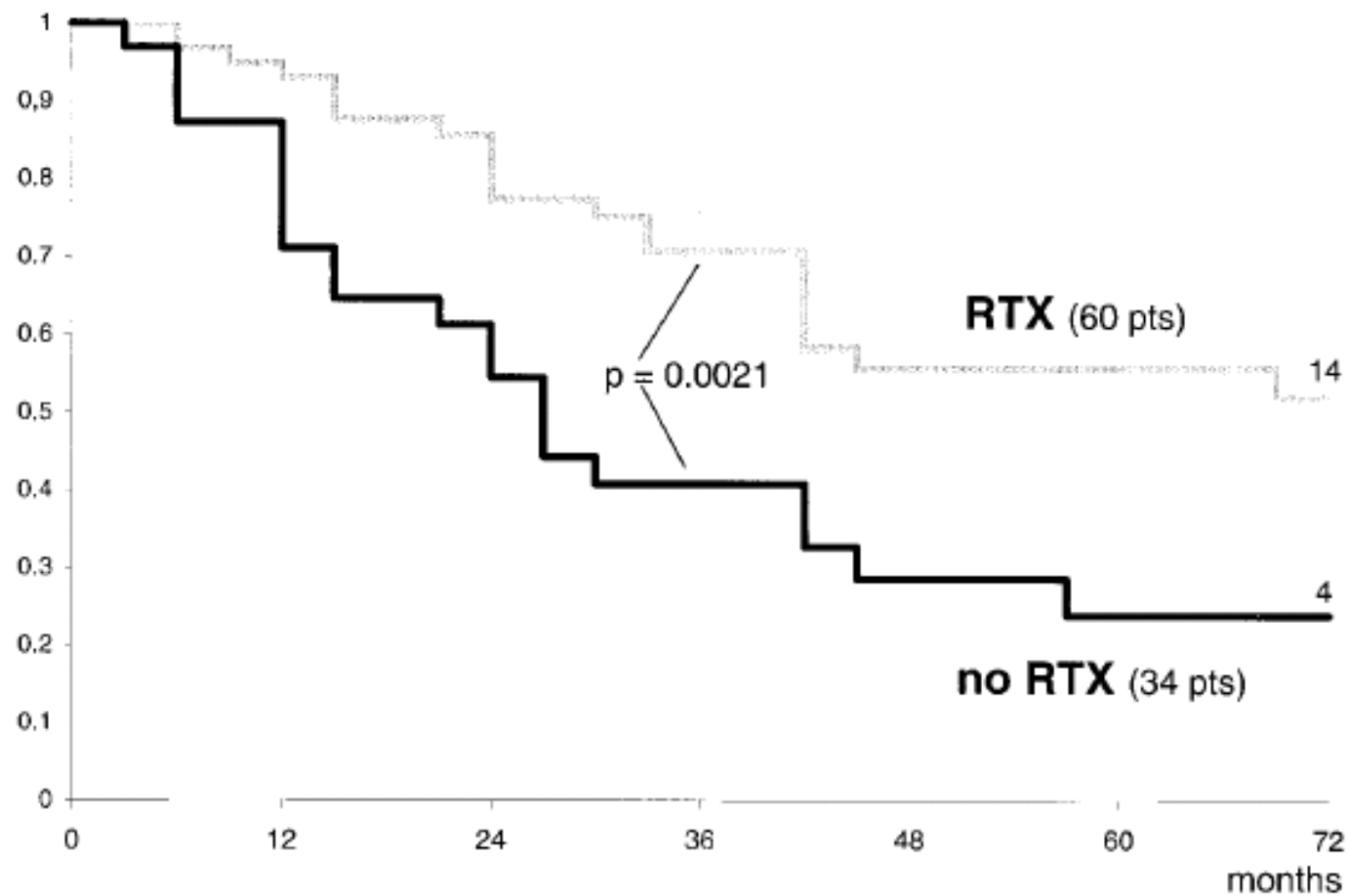
- Stoeckle - *Cancer* 2001 - France
- Retrospective review of 165 pts treated for RP STS
- 84% intermediate or high grade
- R0 obtained in 94 of the 145 non-metastatic pts
- Median dose in RT pts was 50Gy in 28fx
- Median f/u 47 mo.

TABLE 1
Characteristics of Patients and Tumors in 165 Patients

Characteristic	M1 (n = 20)	M0 (n = 145)	Total (n = 165)
Gender (%)			
Male	7	71	78 (47)
Female	13	74	87 (53)
Median age (range)	49 yrs	54 yrs	54 (16–82) yrs
Tumor size			
Mean (range)	10 cm	18 cm	17 (2–70) cm
Median	9 cm	15 cm	15 cm
Tumor location (%)			
Abdomen	12	104	116 (70)
Pelvis	8	41	49 (30)
Classification (%) ^a			
T1	1	8	9 (6)
T2	11	93	104 (63)
T3	7	44	51 (31)
N0	16	141	157 (95)
N1	4	4	8 (5)
Grade (%)			
G1	0	27	27 (16)
G2	6	61	67 (41)
G3	14	57	71 (43)
Histologic subtypes (%)			
Liposarcoma	0	43	43 (26)
Leiomyosarcoma	4	34	38 (23)
MFH	3	25	28 (17)
MPNST	2	11	13 (8)
Rhabdomyosarcoma	5	6	11 (7)
Synovialosarcoma	0	4	4 (2)
Ewing	1	3	4 (2)
Others	4	10	14 (9)
Unclassified	1	9	10 (6)

Univariate analysis risk factor	Excision (no. of patients)		P value
	Complete (%)	Incomplete (%)	
T classification			
T1-2	78 (77)	23 (23)	
T3	16 (36)	28 (64)	<0.0001
Histologic subtypes			
MPNST + Syn. + Rhabd.	5 (24)	16 (76)	
Others	89 (72)	35 (28)	<0.0001
Neoadjuvant (yes)	5 (33)	10 (67)	
Chemotherapy (no)	89 (68)	41 (32)	0.007
Grade			
1	24 (89)	3 (11)	
2	38 (62)	23 (38)	
3	32 (56)	25 (44)	0.012
Localization			
Abdomen	73 (70)	31 (30)	
Pelvis	21 (51)	20 (49)	0.031
Age (yrs)			
< 50	31 (54)	26 (46)	
> 50	63 (72)	25 (28)	0.034
Histologic subtypes			
Liposarcoma	32 (74)	11 (26)	
Others	62 (61)	40 (39)	0.116
Size (cm)			
< 10	28 (72)	11 (28)	
11–19	31 (69)	14 (31)	
> 20	35 (60)	23 (40)	0.454
Gender			
Male	45 (63)	26 (37)	
Female	49 (66)	25 (34)	0.721
Multifocality			
Yes	14 (67)	7 (33)	
No	67 (65)	36 (35)	0.887

FIGURE 3. Local recurrence free intervals after complete excision according to adjuvant radiotherapy: 60 patients with adjuvant radiotherapy (RTX) versus 34 patients without adjuvant radiotherapy (no RTX). pts: patients.



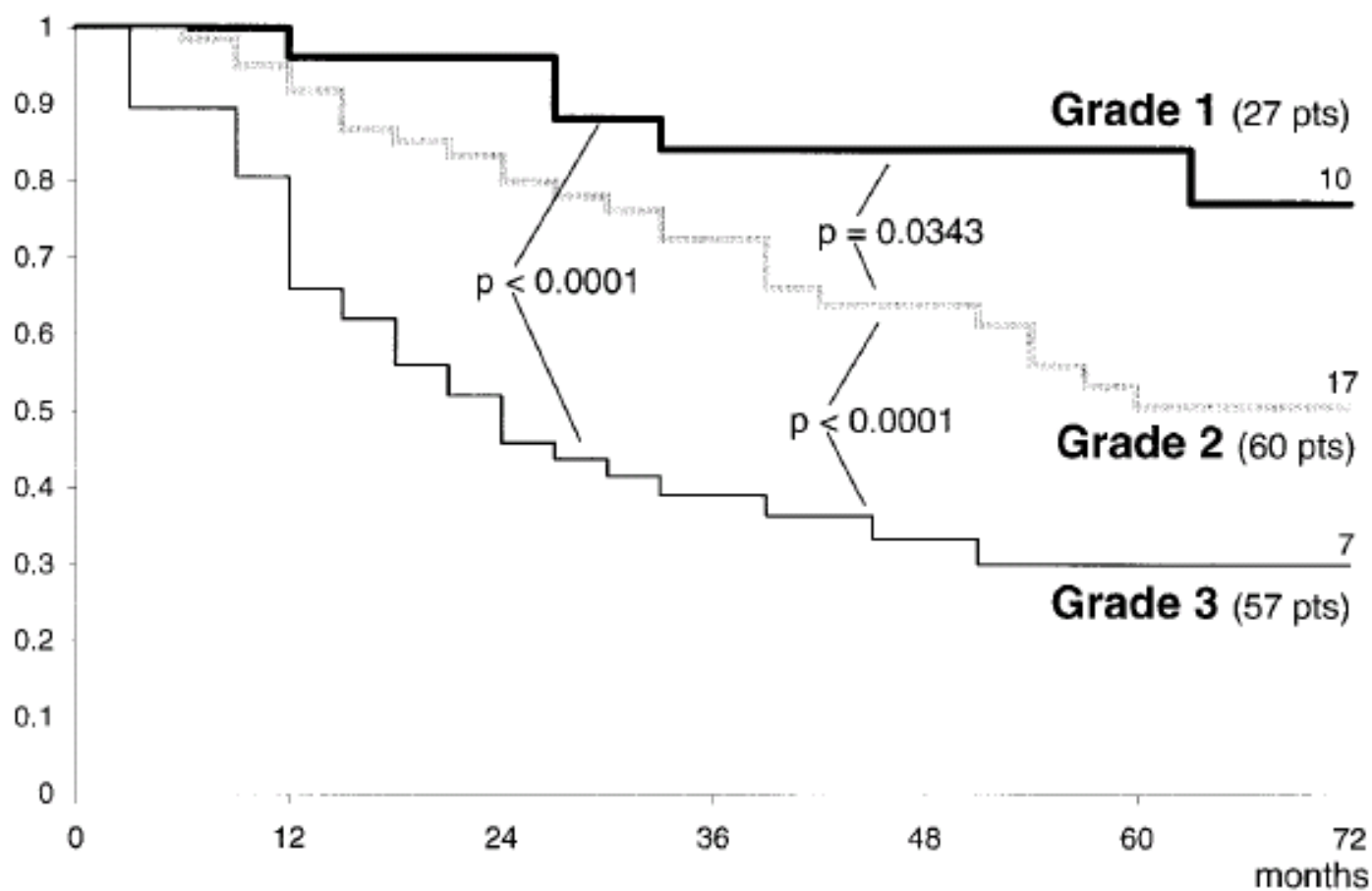


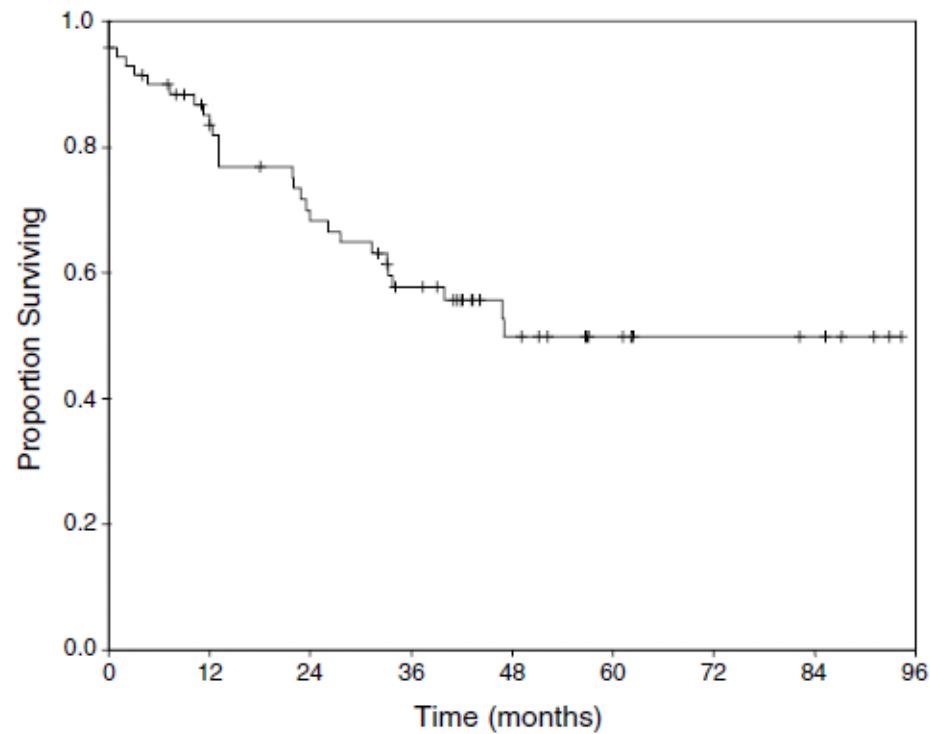
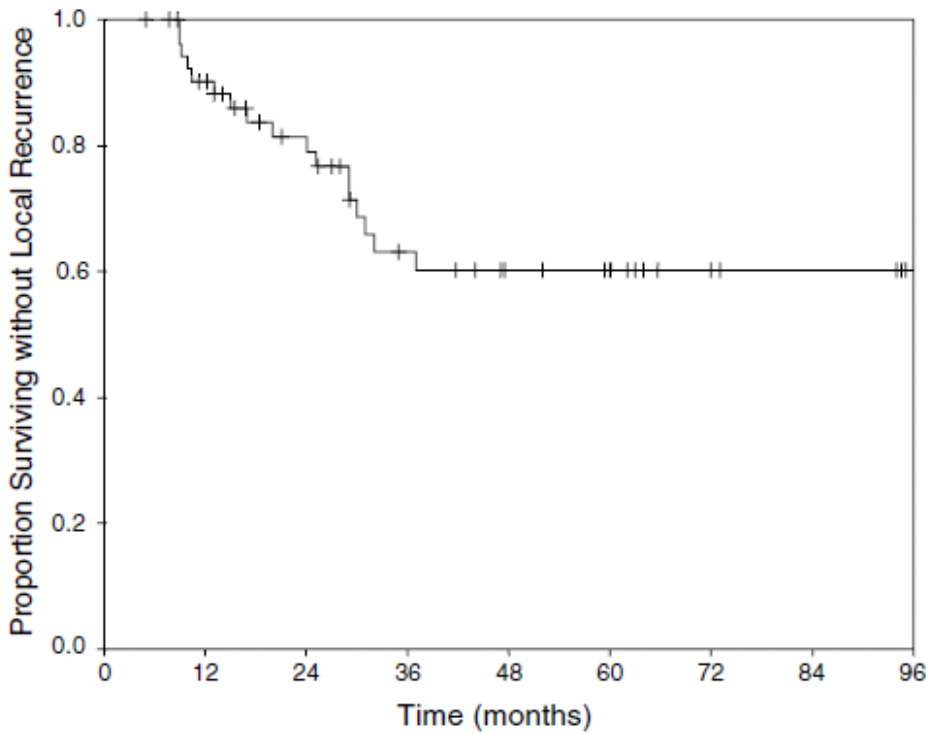
FIGURE 5. Actuarial overall survival according to tumor grade: 27 patients with low-grade tumors (Grade 1) versus 60 patients with intermediate grade tumors (Grade 2) versus 57 patients with high-grade tumors (Grade 3). pts: patients.

TABLE 5
Prognostic Factors for Overall Survival in Patients without Initial Metastases (M0, 145 Patients)

Univariate analysis risk factor	No. of patients	5-yr actuarial OS (%)	<i>P</i> value
Complete remission			
Yes	114	59	
No	29	11	1.2×10^{-7}
Grade			
1	27	70	
2	60	50	
3	57	30	2.1×10^{-6}
T classification			
T1-2	100	60	
T3	44	22	1.7×10^{-5}
Complete excision			
Yes	94	62	
No	50	26	0.0005
Histologic subtype			
Liposarcoma	42	68	
Others	102	39	0.0012
Radiotherapy			
Yes	89	52	
No	55	44	0.0363
Location			
Abdomen	103	45	
Pelvis	41	60	0.1366
Gender			
Male	71	43	
Female	73	56	0.2184
Size (cm)			
< 10	39	47	
11-19	45	47	
> 20	57	52	0.6891

Pre-Op RT

- Pawlik – *Ann Surg Onc* 2006 – MDACC & Toronto
- Pooled results of 2 prospective trials of RP STS treated with pre-op RT
- Median tumor size was 15cm.
- Median pre-op dose was 45Gy. MDACC pts had concurrent doxorubicin 4mg/m² q week.
- IORT or post-op boost in 60%
- R0 or R1 in 95%
- Median f/u 3.4 yr.



-5yr RFS = 60%, 5yr OS = 50%

-**Only 3% rate of significant toxicity (GI)

Pre-Op or Post-Op RT

- Ballo - *IJROBP* 2007 - MDACC
- Retrospective review of 83 pts treated for RP STS
- 84% intermediate or high grade
- Median doses were:
 - Pre-op = 50Gy - Post-op = 55Gy -IORT = 15Gy
- Median f/u 47 mo.

Table 3. Characteristics independently associated with outcomes for patients with RP STS

Survival endpoint	Factor	% at 5 years	<i>p</i> value*
Disease-specific	Low-grade	92	0.006
	Intermediate-grade	51	
	High-grade	41	
Distant metastasis-free	Low-grade	92	0.04
	Intermediate-grade	78	
	High-grade	57	
Local control	Negative resection margin	62	0.01
	Positive resection margin	33	
	Primary disease presentation	58	0.002
	Recurrent disease presentation	27	
	Age ≤65 y	54	0.05
Age >65 y	30		

* Multivariate analysis.

**5-yr toxicity rate was 0% with pre-op RT vs. 23% with post-op RT (p = .006)

-There was no difference in LC or OS for pre-op vs. post-op vs. IORT

IORT

- Sindelar – *Arch Surg* 1993 – NCI
- prospective trial of RP STS treated with IORT (20Gy) + post-op RT (35-40Gy) vs. post-op RT alone (50-55 Gy)
- 35 pts
- Median f/u 8 yr.

Criterion	Median Time, mo		<i>P</i>
	IORT*	Control	
Overall survival	45	52	.39
Disease-free interval	19	38	.58
Time to locoregional recurrence	63	38	.40
Time to in-field local recurrence	>127	38	<.05

*IORT indicates intraoperative radiotherapy.

Table 8.—Complications

Category	Complication	No. of Patients		P
		IORT*	Control	
Cardiovascular	Arterial occlusion	1	2	.99
	Mycotic aneurysm	0	1	.99
	Venous thrombosis	0	1	.99
Pulmonary	Prolonged ventilatory support	0	1	.99
	Pulmonary embolus	1	1	.99
Gastrointestinal	Enteritis			
	Acute	1	12	<.01
	Chronic	2	10	<.05
	Fistula	0	5	.06
	Hemorrhage	1	2	.99
Genitourinary	Ureteral stenosis	2	2	.99
	Ureteral fistula	0	1	.99
	Radiation nephritis	1	5	.21
Neurologic	Neuropathy			
	Mild	2	1	.57
	Moderate to severe	7	0	<.01
Infectious	Wound infection	1	1	.99
	Intra-abdominal abscess	1	6	.20
Other	Skin desquamation	1	3	.62
	Myelosuppression	1	3	.62
	Treatment-related death	1	2	.99

*IORT indicates intraoperative radiotherapy.

RT for MPNST

- Wong - *IJROBP* 1998 - Mayo
- Retrospective review of 134 pts with MPNST (24% w/ NF1)
- 53% had RT
 - 13% had pre-op (median dose 50.4 Gy)
 - 46% had post-op (median dose 50.7 Gy)
 - 12% had IORT (median dose 12.5 Gy)
 - 10% had brachy (median dose 15 Gy)
- Median f/u 53 mo.

Table 2. Prognostic factors for survival

Prognostic factor		% Survival		<i>p</i> Value	
		3-yr	5-yr	Univariate	Multivariate
Size	≤ 5 cm	82	70	< 0.0001	0.24
	5.1–10 cm	61	57		
	10.1–15 cm	48	43		
	> 15 cm	13			
Location	Non-extremity sites	56	43	0.0064	0.20
	Extremities sites	82	70		
History of NF-1	Yes	42	36	0.0074	0.075
	No	70	57		
History of prior irradiation	Yes	28		0.0004	0.023
	No	67	58		
Stage	1	78	65	0.034	
	2	72	60		
	3	58	46		
Grade	1	78	65	0.0074	0.39
	2	74	61		
	3	54	35		
	4	61	55		
Surgical margin	Positive	47	22	0.003	0.0044
	Negative	74	67		
	Close	50	43		
	Unknown	65	37		
Use of IOERT/brachytherapy	Yes	84	72	0.039	0.32
	No	61	50		
Mitotic rate/10 HPF	0–5	78	62	0.040	
	≥ 6	53	41		
Presence of necrosis	Yes	49	37	0.0099	
	No	78	62		
Histologic subtype	Neurofibroma-like	57	36	0.022	0.17
	Primitive	69	45		
	Fibrosarcomatous	51	35		
	Epithelioid	67	44		
	Perineurial	83	83		

Local control rate

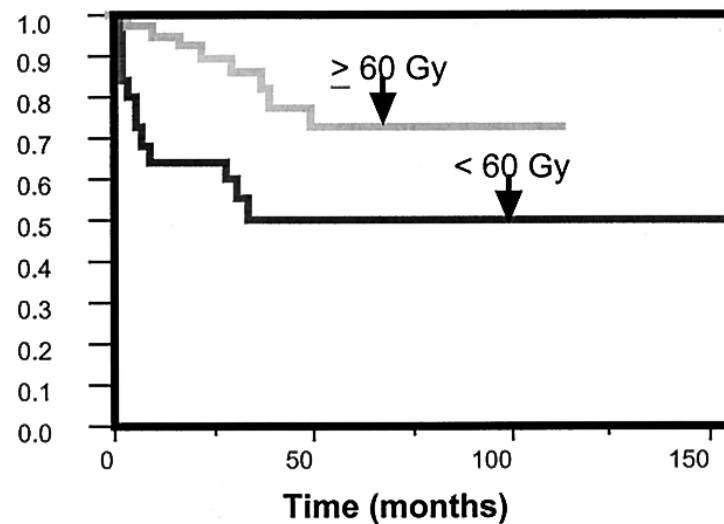


Table 3. Prognostic factors for local control of disease

Prognostic factor		% Local control		<i>p</i> Value	
		3-yr	5-yr	Univariate	Multivariate
Location	Non-extremity sites	51	43	0.016	0.55
	Extremity sites	74	69		
History of NF-1	Yes	40	40	0.026	0.10
	No	62	55		
History of prior irradiation	Yes	8		< 0.0001	0.19
	No	63	55		
Surgical margin	Positive	37	23	< 0.0001	0.0024
	Negative	74	67		
	Close	45	45		
	Unknown	46	39		
Mitotic rate/10 HPF	0–5	71	67	0.005	0.23
	≥ 6	39	32		
Use of radiation therapy	Yes	73	65	0.0004	
	No	40	34		
Dose of irradiation	< 60 Gy	50	50	0.008	0.021
	≥ 60 Gy	87	73		
Use of IOERT/brachytherapy	Yes	94	88	0.002	0.017
	No	59	51		



Table 73.5

OUTCOMES WITH EXTERNAL-BEAM RADIOTHERAPY (EBRT) + INTRAOPERATIVE RADIOTHERAPY (IORT) BOOST FOLLOWING RESECTION OF PRIMARY AND RECURRENT RETROPERITONEAL SARCOMA (RPS)

Study	Median EBRT Dose (Gy)	Median IORT Dose (Gy)	Local Recurrence (%)	Overall Survival (%)	Toxicity (%)
Petersen et al. (38)	Primary RPS: 48.6 (post-op) Recurrent: 45 (post-op)	Primary RPS: 12.5 Recurrent: 15	Primary RPS: 0 (CE), 8 (micro), 40 (gross); 5-yr LC Recurrent: 0 (CE), 64 (micro), 33 (gross)	Primary RPS: 62 (CE), 54 (micro), 29 (gross); 5 yr-OS Recurrent: 80 (CE), 44 (micro), 45 (gross)	Chronic enteritis (16); grade 3-4 GI complications (18); fistula formation (18); neuropathy (mild, 12; moderate/severe, 21)
Sindelar et al. (47)	IORT arm: 35–40 (post-op); EBRT alone arm: 50–55 (post-op)	20	IORT arm: time to in-field local recurrence: >127 mo EBRT alone arm: 38 mo (<i>p</i> < .05)	IORT arm: 45 mo EBRT alone arm: 52 (<i>p</i> = 0.39)	IORT arm: chronic enteritis (13); neuropathy (mild, 13; 47% moderate/severe, 47) EBRT alone arm: Chronic enteritis (50), fistula formation (25); neuropathy (mild, 6; moderate/severe, 0)
Gieschen et al. (15)	45–50.4 (pre-op)	10 (CE), 12.5–15 (micro), 15–20 (gross)	Complete excision: EBRT + IORT: 17 (5 yr); EBRT alone: 39 (5 yr)	Complete excision: EBRT + IORT: 74 (5 yr); EBRT alone: 30 (5 yr)	Neuropathy (19), hydronephrosis (19), vaginal fistula (6), ureteral fistula (6), small bowel obstruction (6)
Alektiar et al. (2)	45–50.4 (post-op)	12–15 (HDR, Ir-192)	Complete excision: EBRT + IORT: 29 (5 yr) primary RPS; 39 (5 yr) recurrent; 44% (5 yr) total IORT alone: NR (5 yr) primary RPS; 67 (5 yr) recurrent; 50% (5 yr) total	Primary RPS: 75 (5 yr) Recurrent: 30 (5 yr)	Bowel obstruction (18), fistula (9), neuropathy (mild, 6; moderate/severe, 0), ureteral injury (3)



**Table 73.4****LOCAL RECURRENCE IN PATIENTS WITH OR WITHOUT POSTOPERATIVE RADIATION THERAPY (PORT) FOLLOWING A COMPLETE RESECTION**

Study	Local Recurrence with PORT (%)	Local Recurrence without PORT (%)	<i>p</i> Value
Ferrario and Karakousis (14)	38 (at 41 mo)	53 (at 41 mo)	0.16
Stoeckle et al. (49)	45 (5 yr)	77 (5 yr)	0.0021
Catton et al. (9)	103 mo to LRF	30 mo to LRF	0.02

Ongoing trials

- Currently there are no open RTOG trials for RP sarcoma
- ACOSOG Z9031 was a trial for RP sarcoma designed to look at neo-adjuvant RT + surgery vs. surgery alone, but it closed due to poor accrual.

Questions?

- Thank you!

- Additional References:

- Halperin, Perez & Brady “Principles and practice of Radiation Oncology” 5th ed.
- AJCC cancer staging handbook 7th ed.
- Hansen and Roach III “Handbook of evidence-based Radiation Oncology” 2nd ed.
- http://en.wikibooks.org/wiki/Radiation_Oncology
- Hall and Giaccia “Radiobiology for the radiologist” 6th ed.