

PERIOPERATIVE TREATMENT IN RETROPERITONEAL SARCOMA

Stefania Kokkali

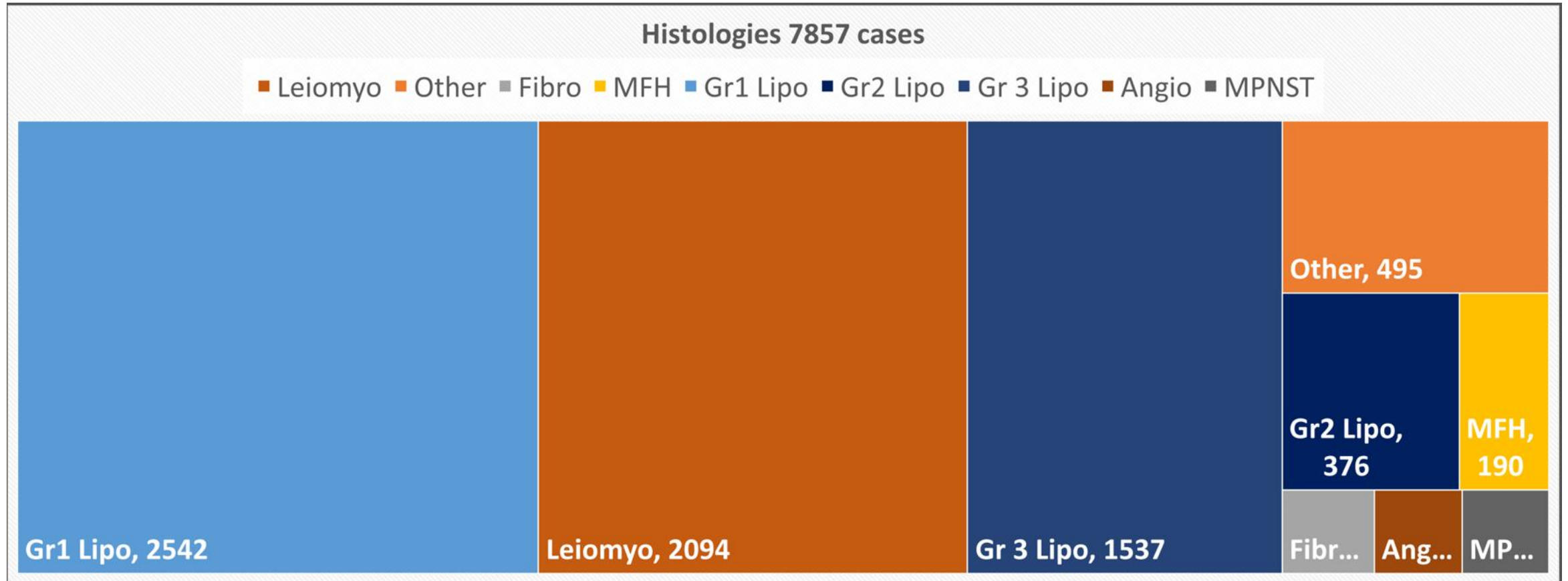
Medical Oncologist,
Hippocratio General Hospital of Athens

14/12/2024

OUTLINE

- Introduction: histology, patterns of recurrence
- Peri-operative chemo
- Peri-operative RT
- Pre-operative chemo-radiation
- Conclusions

Pathology of retroperitoneal sarcomas

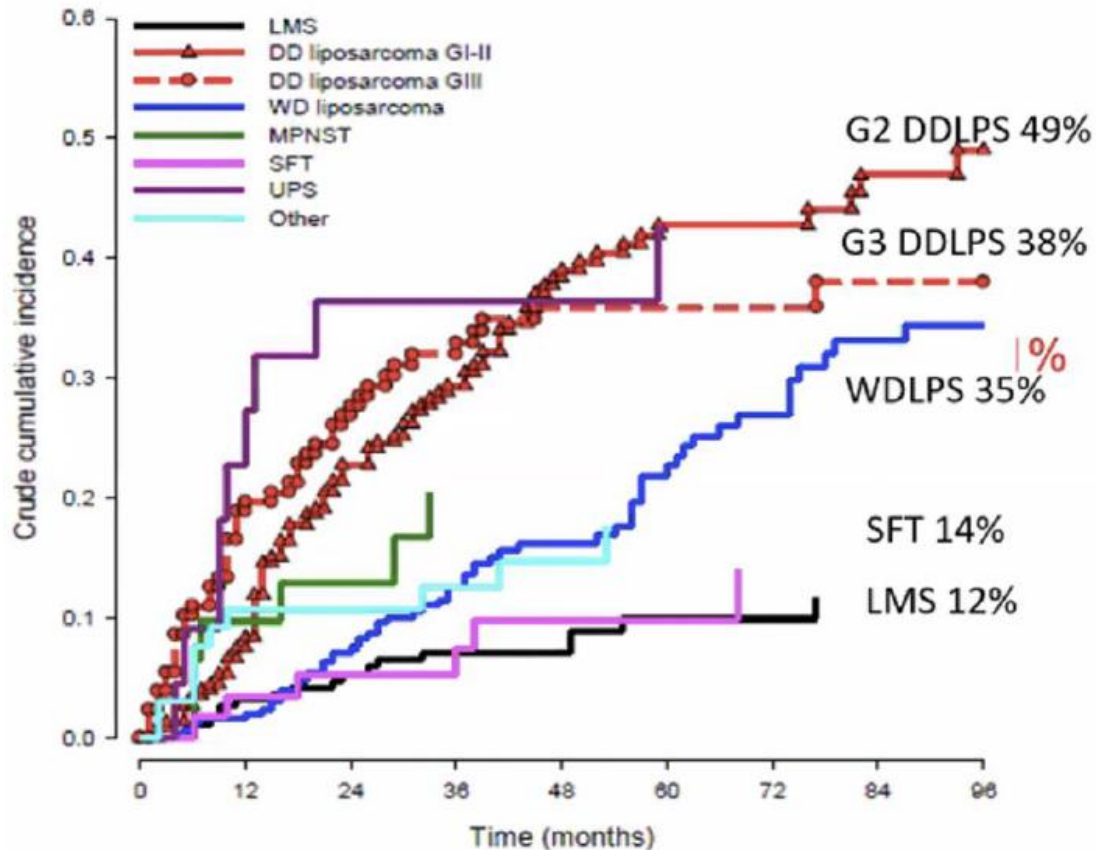


Local relapse rather than metastases

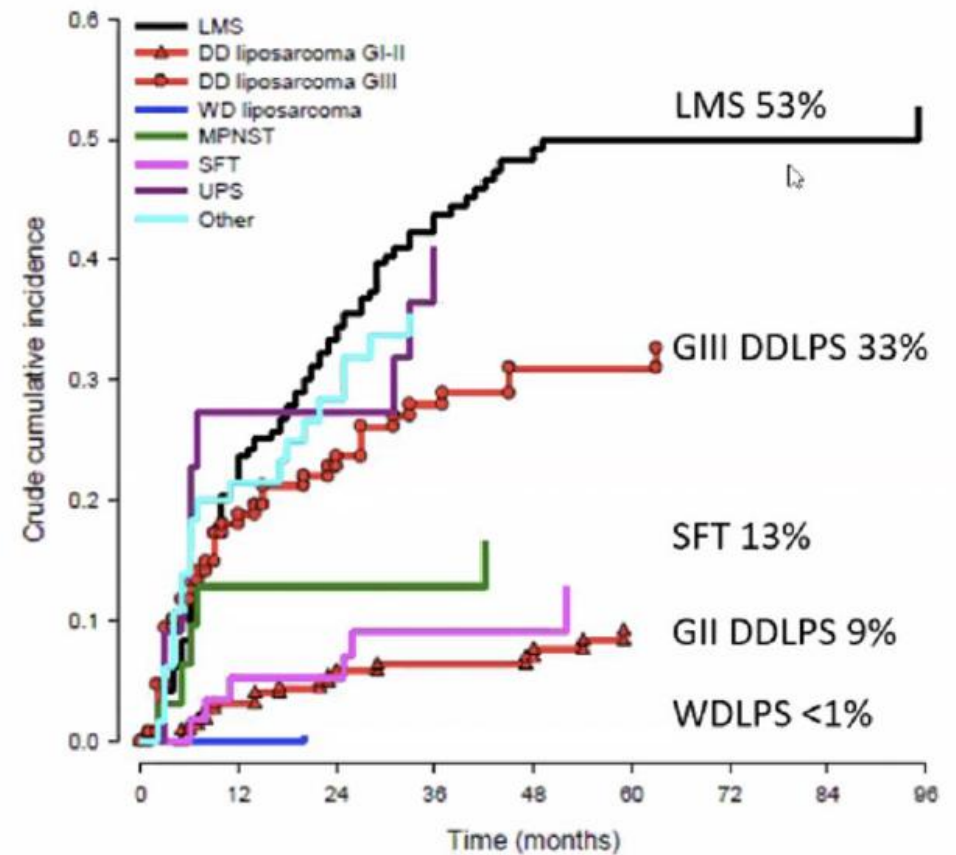
Multi-institutional Collaborative RPS Working Group

1007 patients

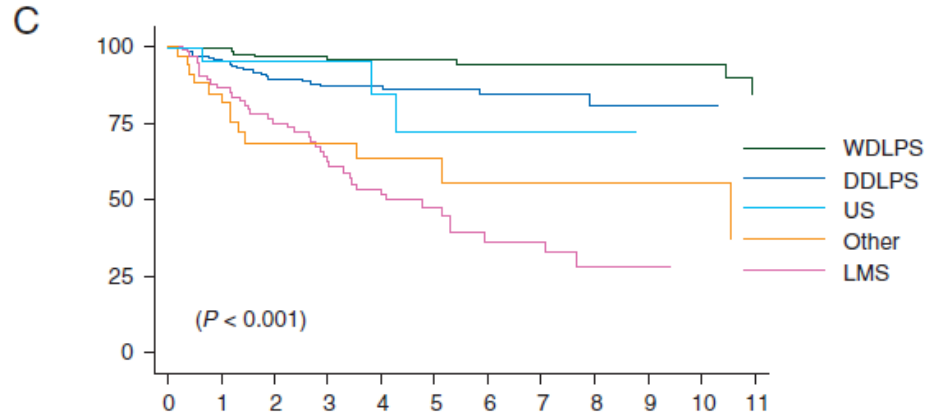
Local Recurrence



Distant Metastasis

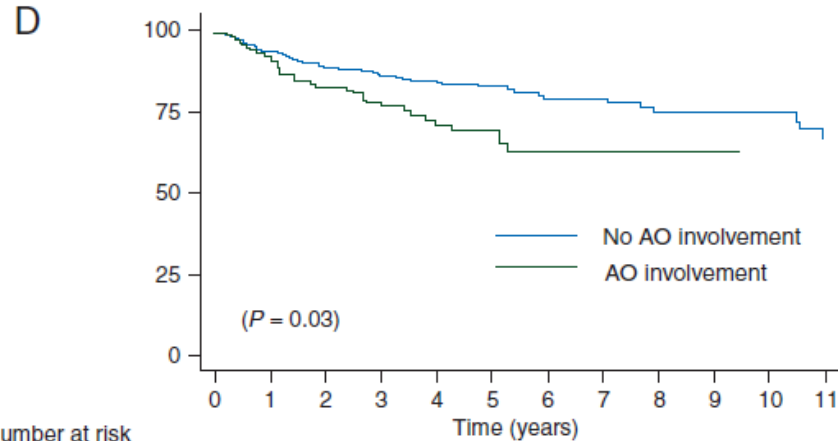


French retrospective study of 586 localized RPS



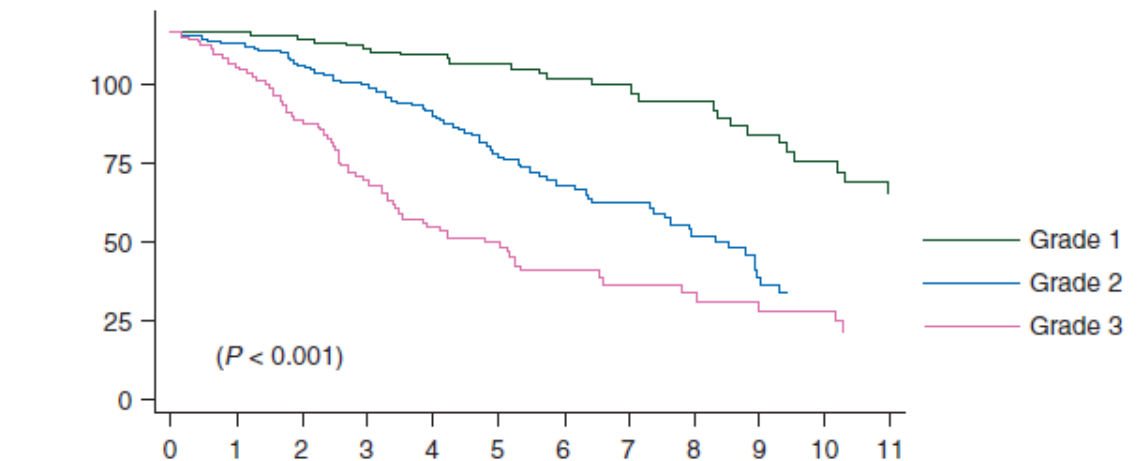
Number at risk	Time (years)											
	0	1	2	3	4	5	6	7	8	9	10	11
DDLPS	156	143	127	104	78	55	39	31	24	15	12	10
WDLPS	103	102	98	94	81	60	47	38	34	28	21	15
LMS	75	62	52	38	28	18	11	9	5	4	3	3
US	21	19	16	12	7	4	1	1	1	0	0	0
Other	34	27	18	14	10	8	4	4	4	3	3	2

Distant metastasis-free survival.



Number at risk	Time (years)											
	0	1	2	3	4	5	6	7	8	9	10	11
No AO involvement	244	225	207	185	150	106	75	62	51	38	32	24
AO involvement	134											

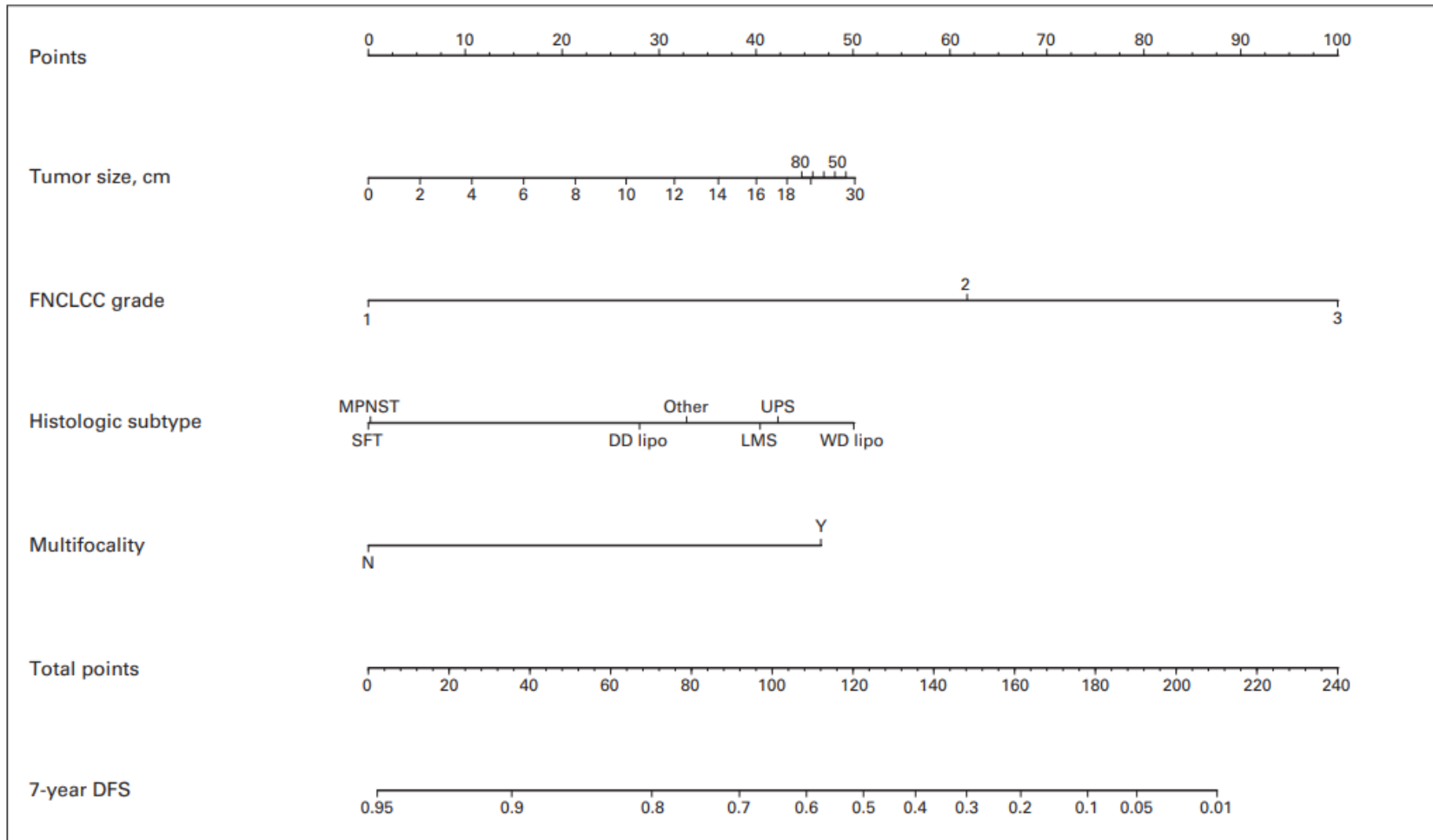
OS



Number at risk	Time (years)											
	0	1	2	3	4	5	6	7	8	9	10	11
Grade 1	114	113	110	104	91	66	50	40	36	30	23	18
Grade 2	154	147	137	122	96	66	49	39	29	16	12	12
Grade 3	117	106	88	65	43	34	19	14	12	10	8	6

Toulmonde et al., 2014

Nomogram for 7-year disease-free survival (DFS) in patients with retroperitoneal soft tissue sarcoma



Variable	backward selection) for OS and DFS					
	OS			DFS		
	HR	95% CI	P*	HR	95% CI	P*
Patient's age, years						
67 v 48†	1.34	1.04 to 1.71	.016	—†	—†	—†
Tumor size, cm						
26 v 10†	2.30	1.58 to 3.36	< .001	1.64	1.21 to 2.23	.006
FNCLCC grade						
II v I	11.72	4.30 to 31.93	< .001	3.80	1.87 to 7.72	< .001
III v I	26.82	9.24 to 77.88		8.70	4.14 to 18.26	
Histologic subtype						
LMS v DD lipo	1.49	0.92 to 2.40		1.31	0.88 to 1.95	
WD lipo v DD lipo	3.05	1.26 to 7.40		1.61	0.78 to 3.32	
MPNST v DD lipo	0.93	0.31 to 2.82	.052	0.55	0.20 to 1.54	.183
UPS v DD lipo	1.79	1.13 to 2.85		1.36	0.89 to 2.09	
SFT v DD lipo	0.77	0.18 to 3.25		0.55	0.20 to 1.53	
Other v DD lipo	1.56	0.86 to 2.85		1.11	0.61 to 2.02	
Multifocality						
Yes v no	2.40	1.44 to 4.02	< .001	2.75	1.58 to 4.76	< .001
Extent of resection						
Incomplete v complete	1.70	1.05 to 2.75	.030	—†	—†	—†

Fig 3. Nomogram for 7-year disease-free survival (DFS) in patients with retroperitoneal soft tissue sarcoma. Instructions: The nomogram allows the user to obtain the 7-year DFS probability corresponding to a patient's combination of covariates. For instance, locate the patient's tumor size and draw a line straight upward to the "Points" axis to determine the score associated with that size. Repeat the process for French National Federation of the Centers for the Fight Against Cancer (FNCLCC) grade, histologic subtype, and multifocality, sum the scores achieved for each covariate, and locate this sum on the "Total Points" axis. Draw a line straight down to the "7-year DFS" axis to find the predicted probability. DD lipo, dedifferentiated liposarcoma; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibrous tumor; UPS, undifferentiated pleomorphic sarcoma; WD lipo, well-differentiated liposarcoma.

Why should I consider peri-operative therapy?

- Surgery (resection with negative margins) is the standard-of-care
- May not be possible in all anatomic sites, constrained based on surrounding normal structures and/or lack of resectable normal tissue
- Recurrence in $\leq 50\%$ of cases

Peri-operative chemotherapy

Retropetinoneal sarcomas- ESMO Guidelines 2021

Neoadjuvant treatment, in the form of ChT, external beam RT (EBRT), regional hyperthermia or combinations, can be considered in the case of technically unresectable/ borderline resectable, i.e. RPS that could be surgically converted by downsizing, and in chemosensitive histologies such as synovial sarcoma.²⁶

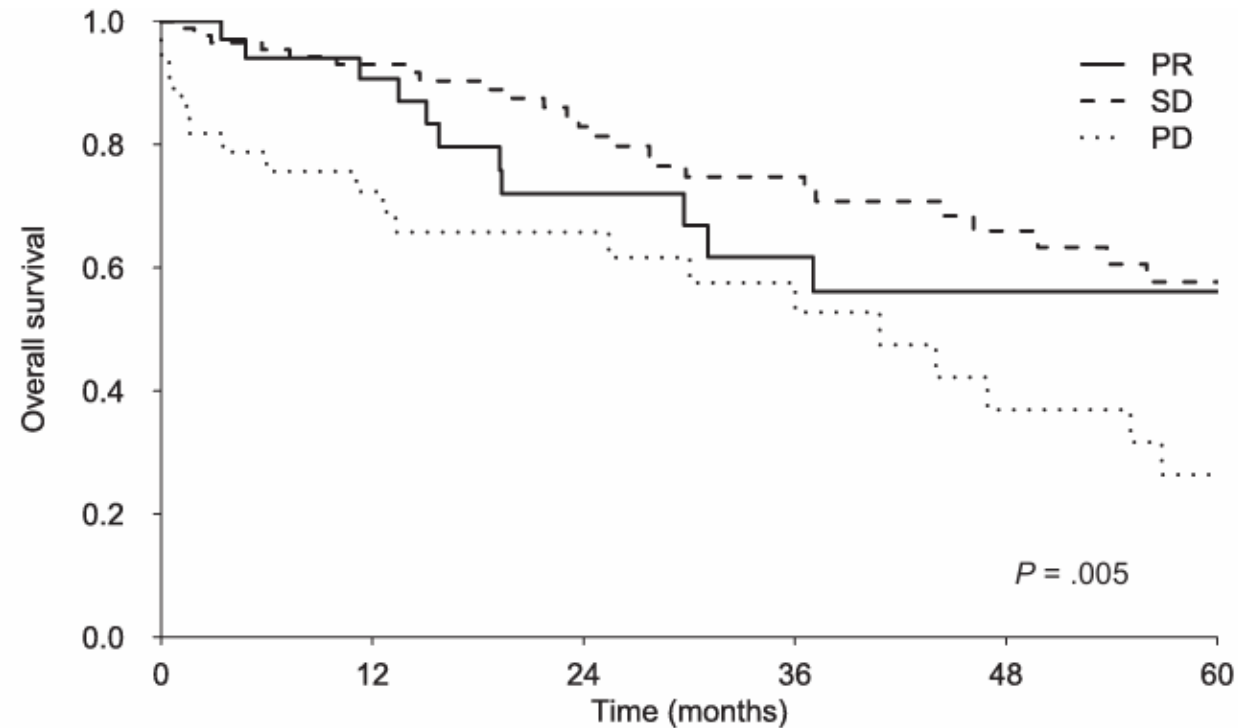
The value of adjuvant/neoadjuvant ChT is not established, though the rarity of the subtypes of RPSs forces extrapolation of the data available in other settings.

Defining the Role of Neoadjuvant Systemic Therapy in High-Risk Retroperitoneal Sarcoma: A Multi-Institutional Study From the TARSWG

TABLE 3. RECIST 1.1 Tumor Responses by Histologic Subtype

	PR, No. (%)	SD, No. (%)	PD, No. (%)
DD	14 (19.7)	37 (52.1)	20 (28.2)
LMS	12 (24.0)	28 (56.0)	10 (20.0)
WD	3 (21.4)	11 (78.6)	0 (0.0)
UPS	5 (45.5)	5 (45.5)	1 (9.1)
MPNST	1 (16.7)	4 (66.7)	1 (16.7)
SFT	2 (33.3)	3 (50.0)	1 (16.7)

In total: PR 23%, SD 56%, PD 21%



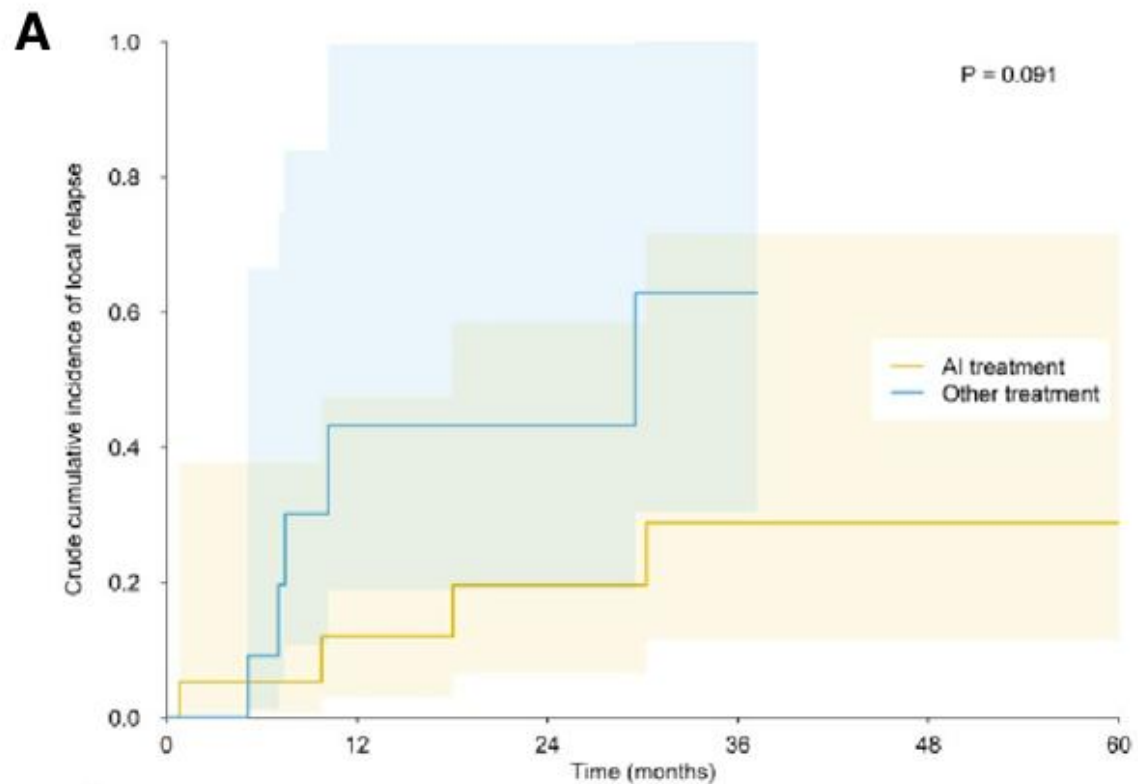
No. pts at risk	0	12	24	36	48	60
PR	37	27	17	12	9	5
SD	88	74	53	38	25	19
PD	33	22	16	12	7	4

Figure 3. Kaplan-Meier curves of overall survival for patients with retroperitoneal sarcoma according to the radiologic tumor response to neoadjuvant systemic therapy (Response Evaluation Criteria in Solid Tumors, version 1.1). PD indicates progressive disease; PR, partial response; SD, stable disease.

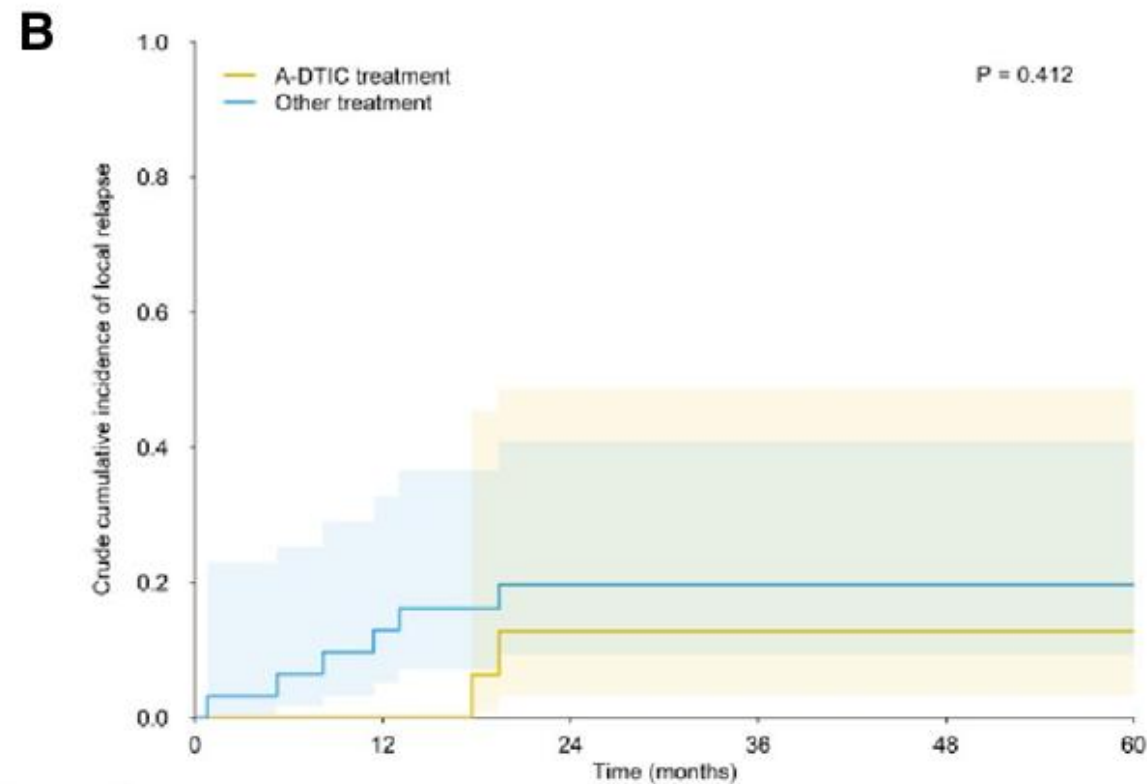
Local recurrence

G3 DD

LMS

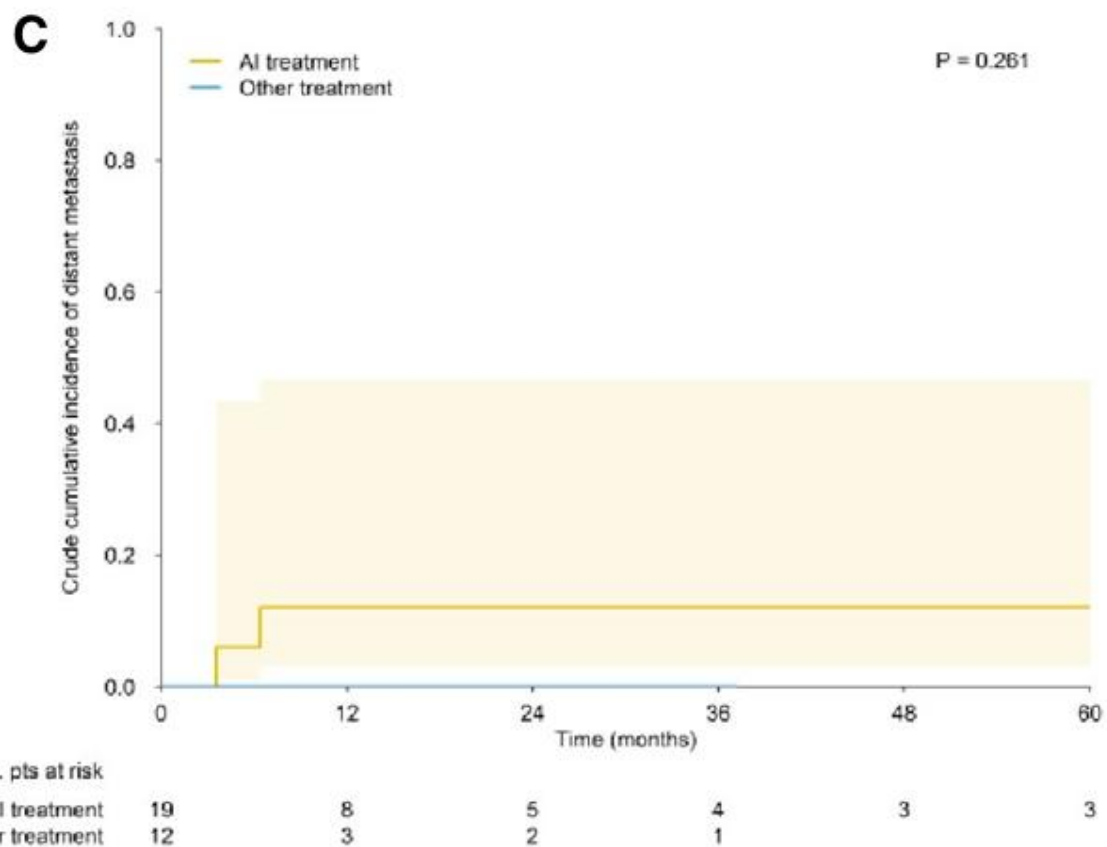


No. pts at risk	0	12	24	36	48	60
AI treatment	19	8	5	4	3	3
Other treatment	12	3	2	1		

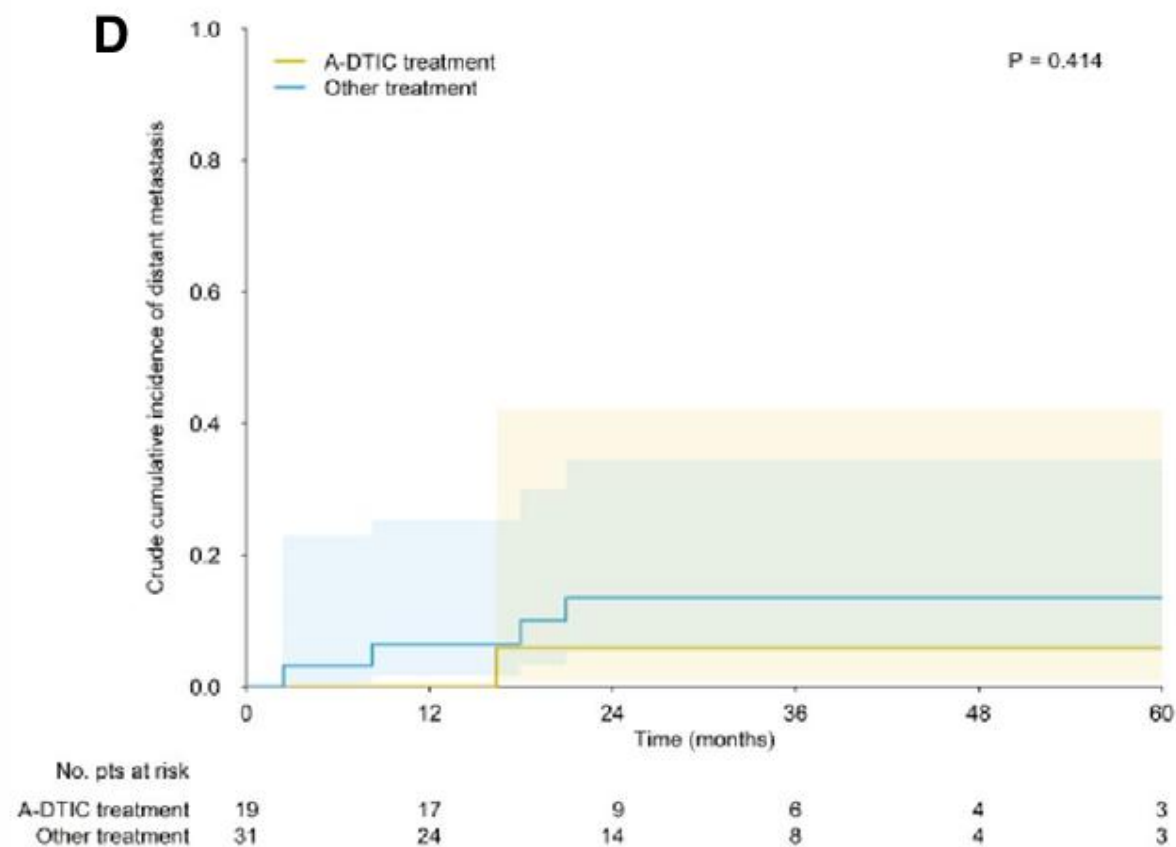


No. pts at risk	0	12	24	36	48	60
A-DTIC treatment	19	17	9	6	4	3
Other treatment	31	24	14	8	4	3

Distant metastases

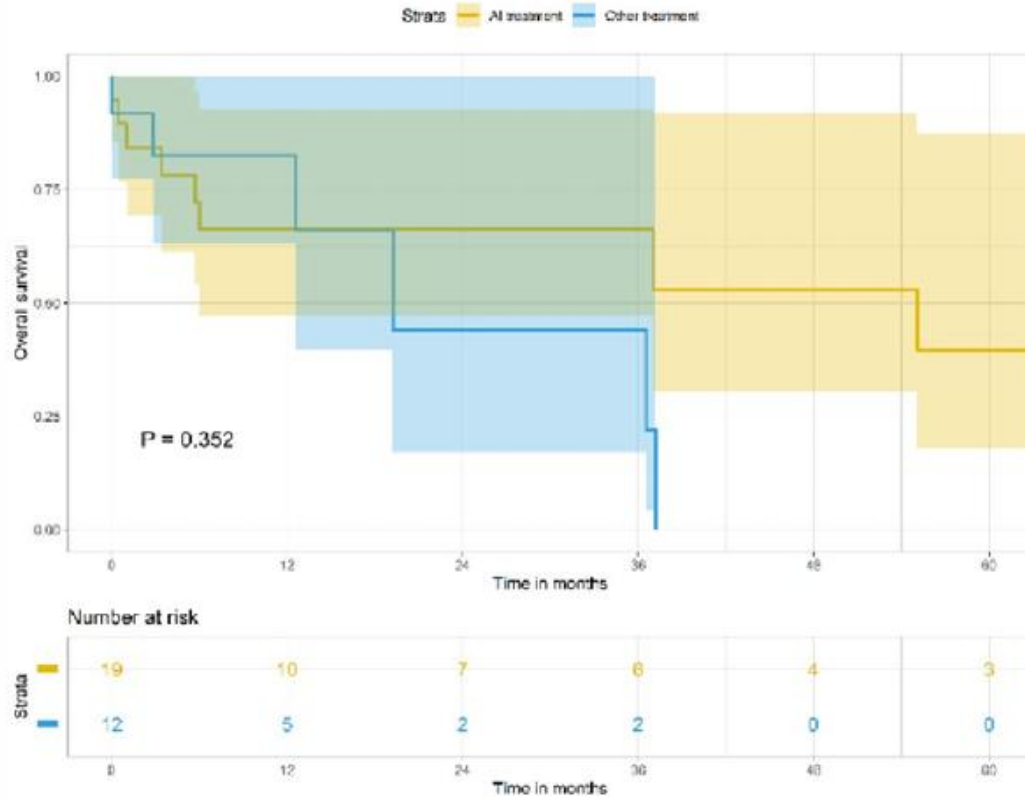


G3 DDLPS

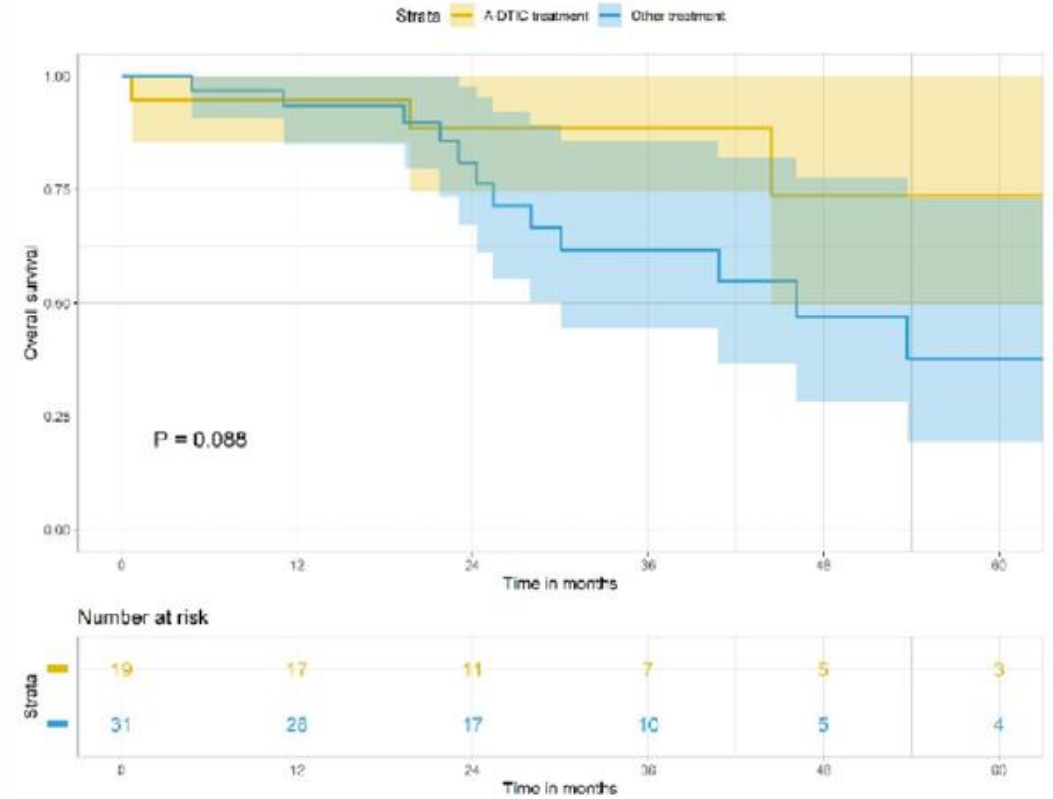


LMS

OS



G3 DDLPS



LMS

Impact of chemotherapy on survival in surgically resected retroperitoneal sarcoma

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A. Banerjee^c, F.M. Johnston^a, K.K. Turaga^{a,*}

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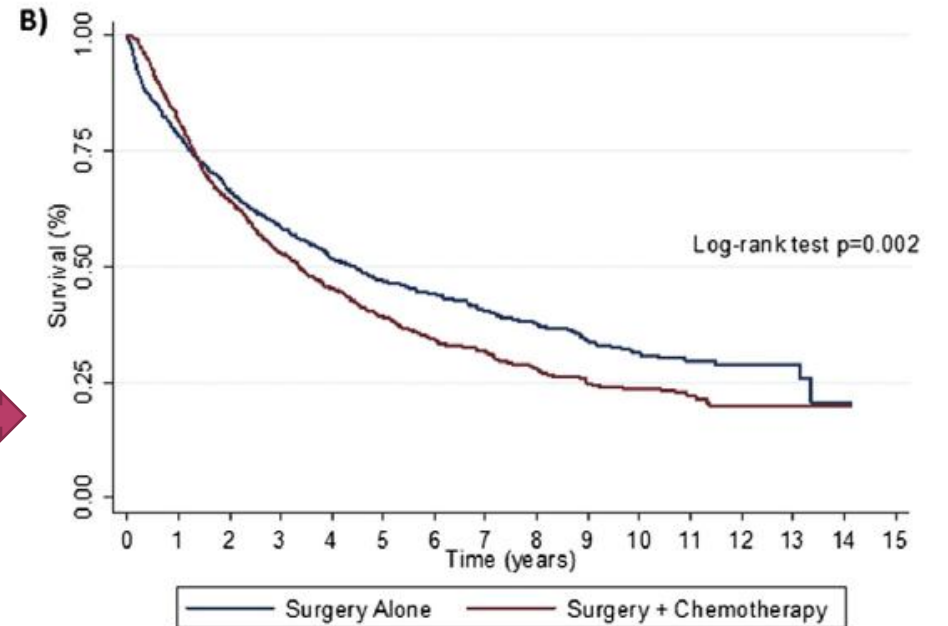
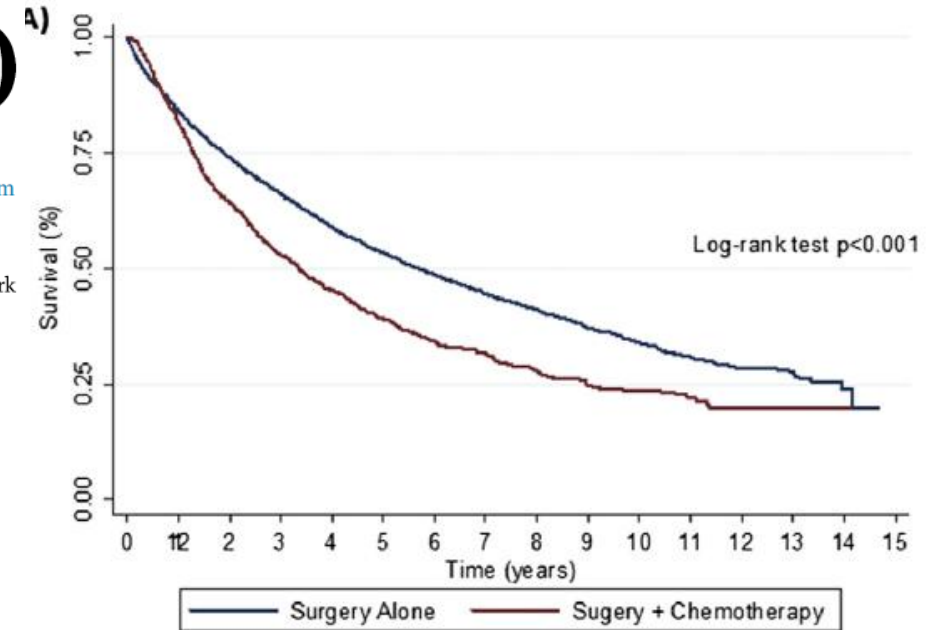
^bDivision of Medical Oncology, Medical College of Wisconsin, Milwaukee, WI, USA

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Accepted 16 July 2015

- Retrospective USA study
- N=8653 operated pts, 17% chemo, 10% neoadj chemo

After propensity score matching to create balanced cohorts for analysis



15 RCT
9281 adjuvant therapy and
21,583 surgery alone cases

RESEARCH

Open Access



Adjuvant therapy for retroperitoneal sarcoma: a meta-analysis

Table 2 Summary of results

Categories	Studies	Patients	Model	HR (95%CI)			Heterogeneity		
				value	z	P-value	X ²	I ²	P-value
OS									
Adjuvant radiotherapy	14	20,564	Fixed	0.80 (0.76–0.84)	8.66	<0.0001	14.86	13%	0.32
Adjuvant chemotherapy	6	9342	Random	1.11 (0.95–1.29)	1.32	0.19	12.08	59%	0.03
Sensitivity analysis of adjuvant chemotherapy	5	5450	Fixed	1.19 (1.08–1.30)	3.68	0.0002	1.35	0%	0.85
RFS									
Adjuvant radiotherapy	4	1454	Fixed	0.61 (0.47–0.79)	3.78	0.0002	1.27	0%	0.74
Adjuvant chemotherapy	2	1238	Fixed	1.30 (0.96–1.77)	1.68	0.09	0.04	0%	0.85
LR									
Adjuvant radiotherapy	2	215	Random	0.31 (0.13–0.71)	2.78	0.005	2.78	54%	0.14
MFS									
Adjuvant chemotherapy	2	1238	Fixed	0.69 (0.45–1.06)	1.69	0.09	0.04	0%	0.84

CI, confidence interval; HR, hazard ratio; LR, local recurrence; OS, overall survival; RFS, recurrence-free survival

Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma

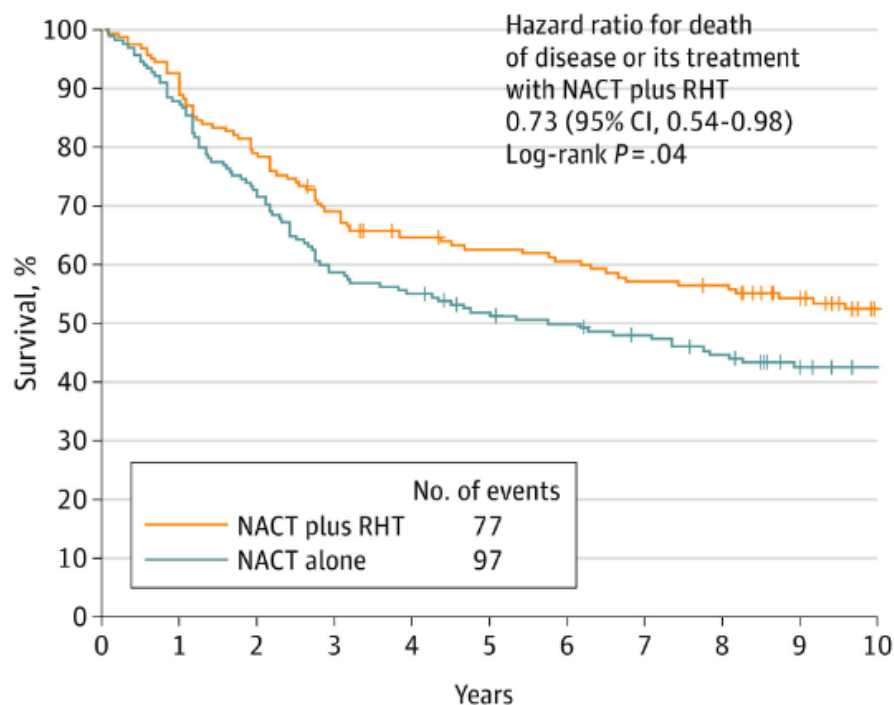
45% RPS

The EORTC 62961-ESHO 95 Randomized Clinical Trial

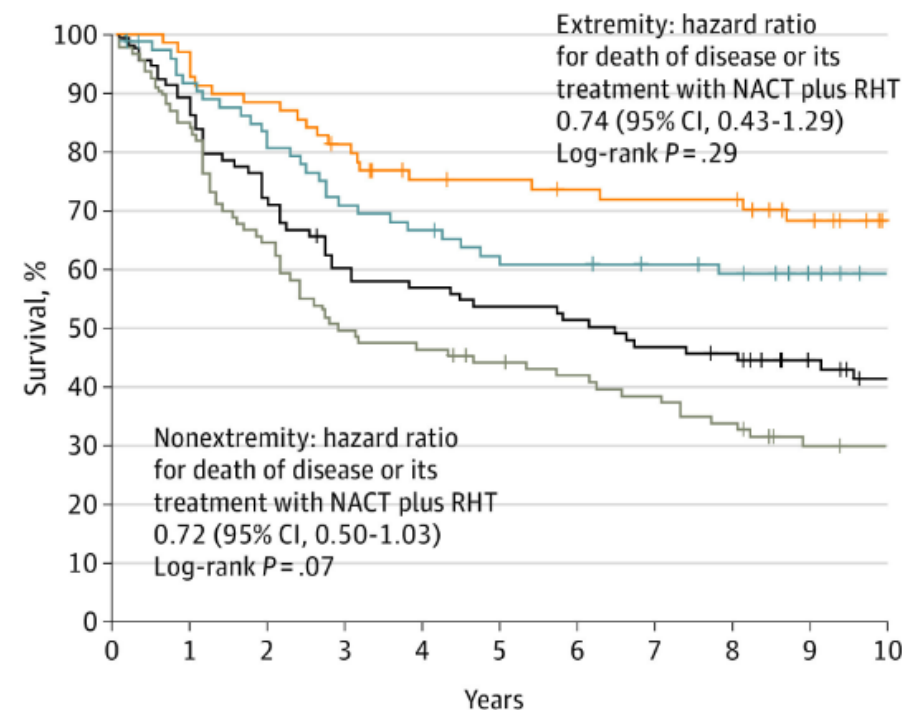
Rolf D. Issels, MD, PhD,¹ Lars H. Lindner, MD,¹ Jaap Verweij, MD,² Rüdiger Wessalowski, MD,³ Peter Reichardt, MD,⁴ Peter Wust, MD,⁵ Pirus Ghadjjar, MD,⁵ Peter Hohenberger, MD,⁶ Martin Angele, MD,⁷ Christoph Salat, MD,¹ Zeljko Vujaskovic, MD,⁸ Soeren Daugaard, MD,⁹ Olav Mella, MD,¹⁰ Ulrich Mansmann, MD,¹¹ Hans Roland Dürr, MD,¹² Thomas Knösel, MD,¹³ Sultan Abdel-Rahman, PhD,¹ Michael Schmidt, MD,¹⁴ Wolfgang Hiddemann, MD,¹ Karl-Walter Jauch, MD,⁷ Claus Belka, MD,¹⁵ and Alessandro Gronchi, MD¹⁶, for the European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology

	No. of events
NACT plus RHT extremity	22
NACT alone extremity	31
NACT plus RHT nonextremity	55
NACT alone nonextremity	66

C Survival

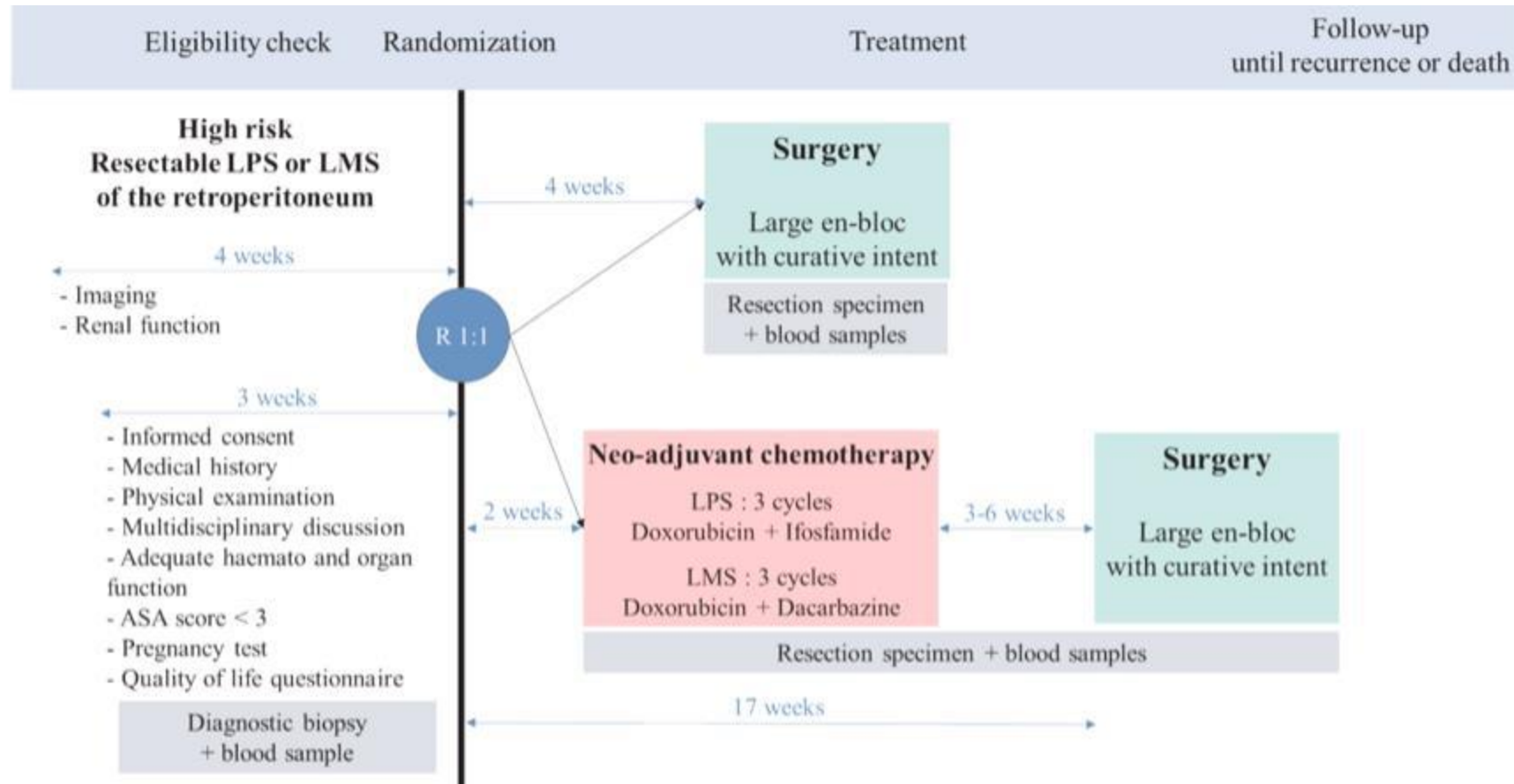


D Extremity vs nonextremity



Intergroup Study 1809-STBSG

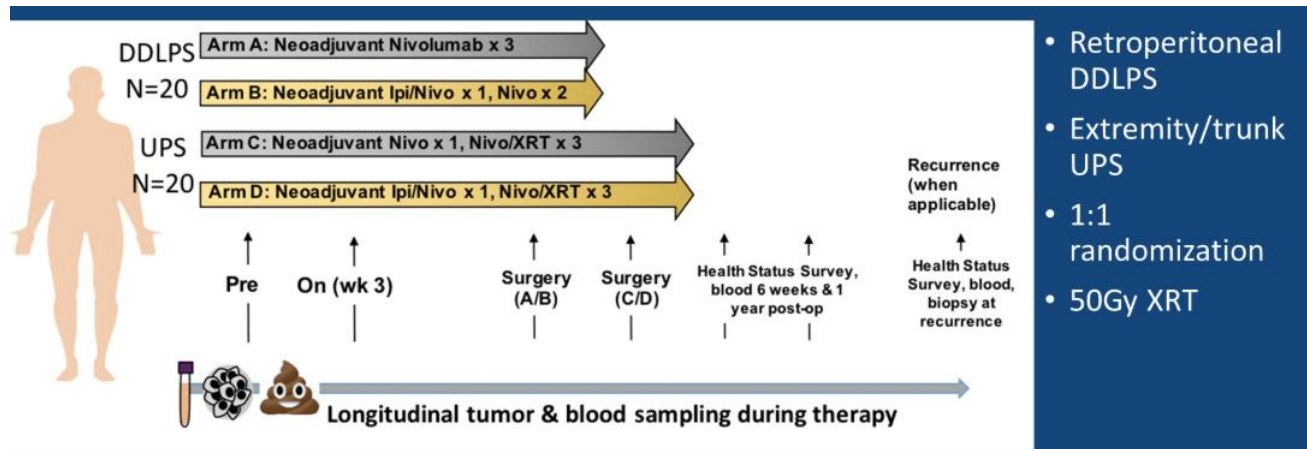
A randomized phase III study of neoadjuvant chemotherapy followed by surgery versus surgery alone for patients with High Risk RetroPeritoneal Sarcoma (STRASS 2)



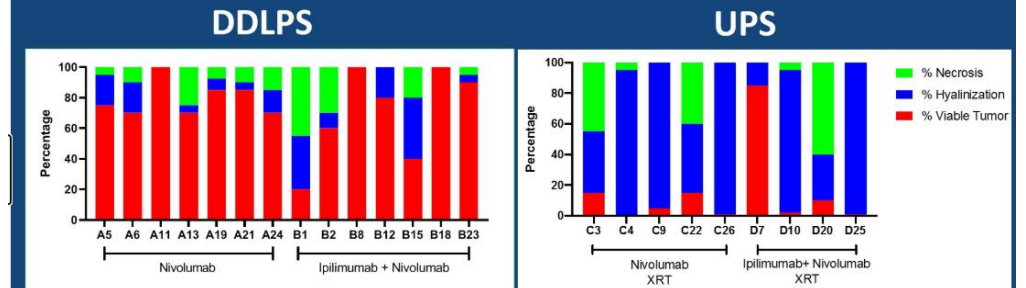
Phase II study of neo-adjuvant IO + RT

- Nivolumab (3 mg/kg) + Ipilimumab (1 mg/kg) ḡ Nivolumab q14d + RT
- 14 UPS extremities/trunkal, 9 RP DDLPS
- 4 independent non-comparative studies (MD Anderson)

Pathologic response: % Hyalinization



Significant Pathologic Response in UPS patients



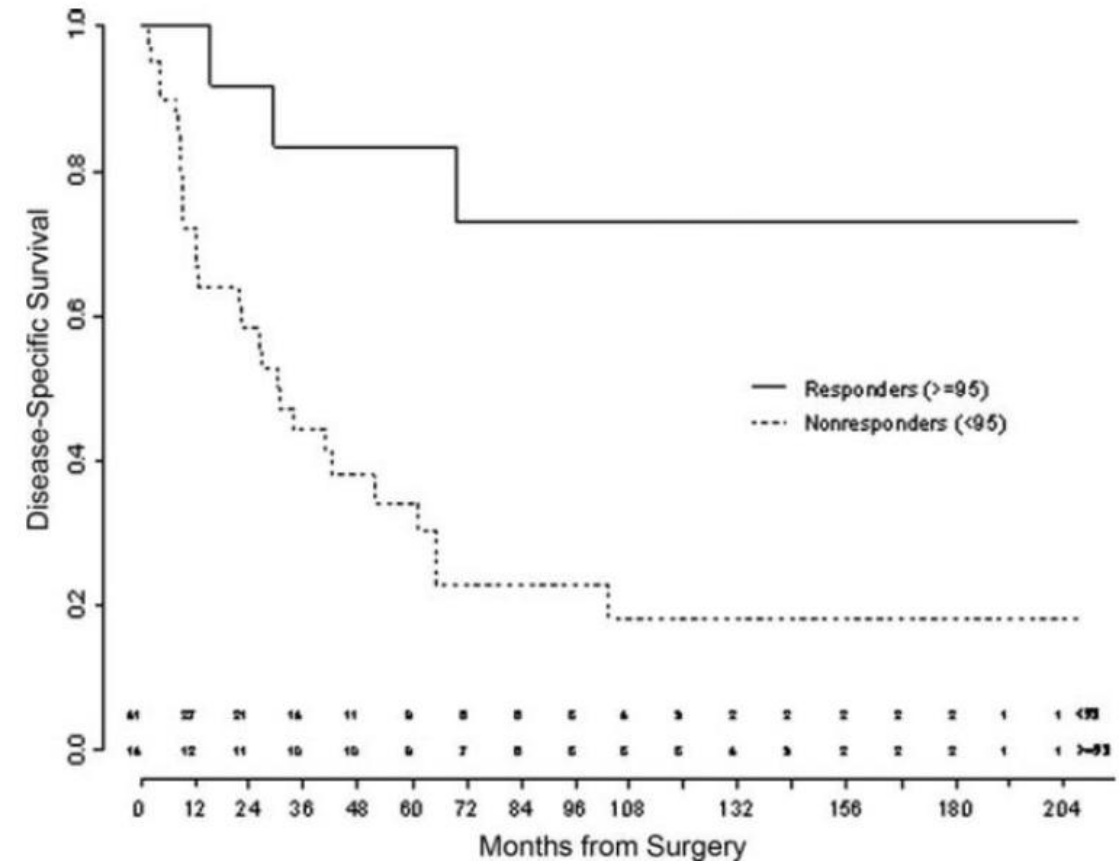
Median hyalinization: 8.75% (range 0-40)
 5/14 (35.7%) patients >20% hyalinization

Median hyalinization: 93% (range 15-99)
 5/9 (56%) patients >95% hyalinization

- viable tumor: 5% in UPS and 77.5% in DDLPS
- no correlation between pathologic and imaging response (RECIST)
- Feasible therapy

Pathological response and DFS

- 55pts (1987-2007) with G3 RPS, UCLA
- $\geq 95\%$ pathologic necrosis=responders
- Different chemo regimens
- 25% of responders
- No effect of chemo on DSS
- 5-year DFS in responders 83%
v. 34% in non-responders
- But 31 pts received also preoperative RT



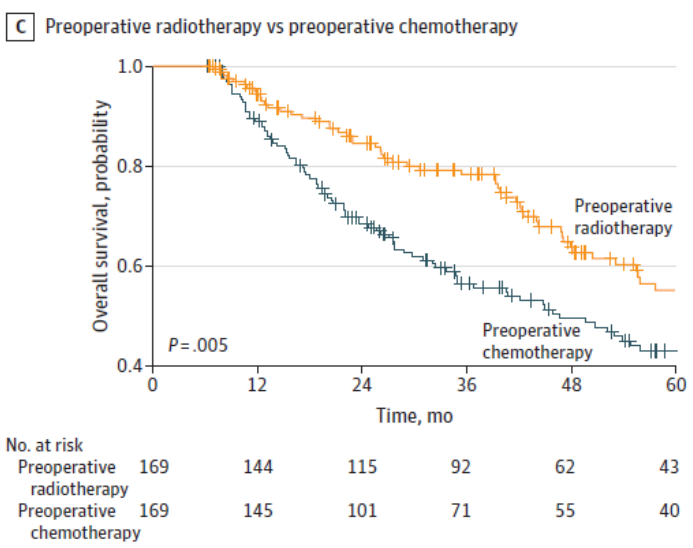
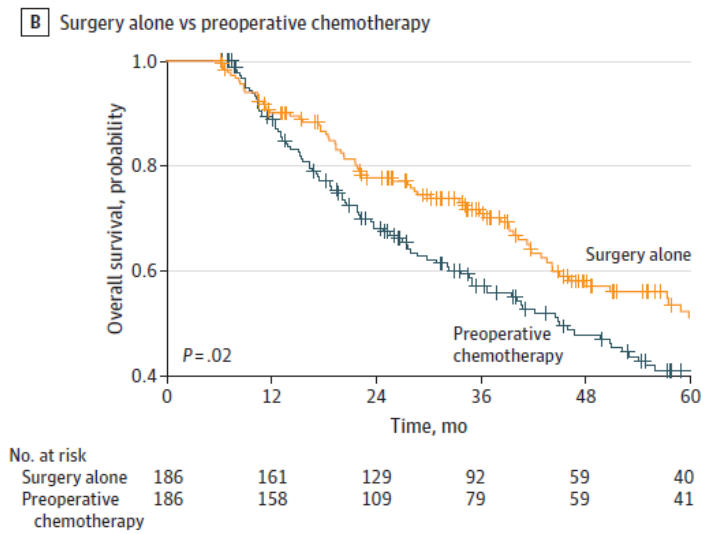
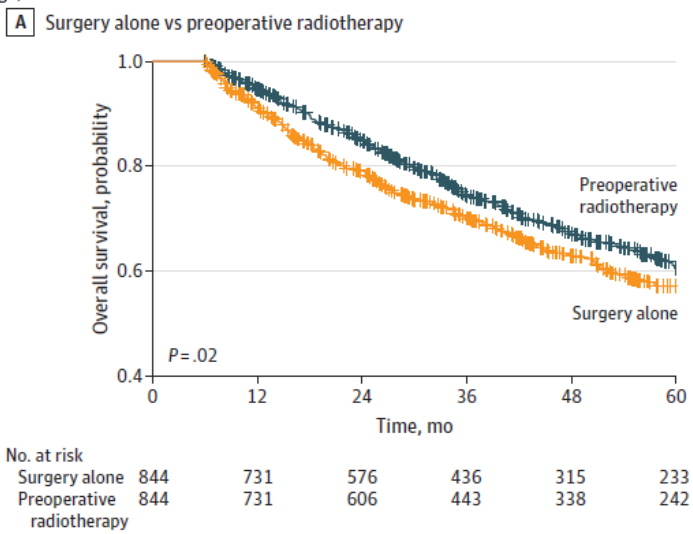
Peri-operative Radiation therapy

Evaluation of Preoperative Chemotherapy or Radiation and Overall Survival in Patients With Nonmetastatic, Resectable Retroperitoneal Sarcoma

Sung Jun Ma, MD; Oluwadamilola T. Oladeru, MD, MA; Mark K. Farrugia, MD, PhD; Rohil Shekher, MD; Austin J. Iovoli, MD; Anurag K. Singh, MD

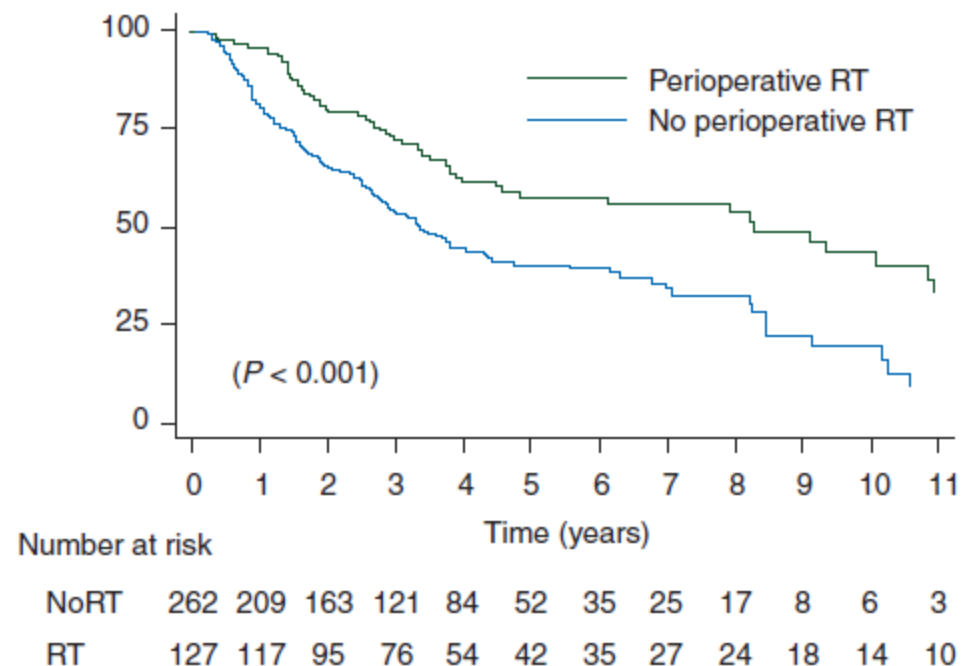
- Retrospective
- USA national registry database
- N=7857
- 86.7% surgery alone, 10.8% preoperative RT, 2.5% preoperative chemo
- Preop RT → improved OS (HR, 0.88; p = 0.03)

Survival Curves After Matching



Locoregional relapse-free survival

Multivariate analysis of factors significantly associated with risk of LR relapse, abdominal sarcomatosis (at 3 years), distant metastasis and overall survival in patients with initial complete resection of primary localized RPS (n = 389)



LR relapse	HR	[95% CI]	P	Abdominal sarcomatosis			Distant metastasis				
				HR ^a	[95% CI]	P	HR	[95% CI]	P		
Male gender	1.5	[1.1–2.0]	0.006	Grade	not Retained	0.13	Histology (<i>WDLPS</i>)				
							DDLPS	2.6	[1.1–6.2]	<0.001	
							LMS	11.9	[5.3–27]		
AO involvement	1.6	[1.2–2.1]	0.004	AO involvement	2	[1.2–3.5]	0.009	US	3.1	[0.8–12]	
Specialized surgeon	0.5	[0.4–0.7]	<0.001	Specialized surgeon	0.5	[0.3–0.9]	0.02	Other	9.6	[3.8–24]	
Piecemeal resection	2.9	[1.9–4.5]	<0.001	Piecemeal resection	4.4	[2.4–8.1]	<0.001	AO involvement	1.6	[1–2.5]	0.03
Perioperative RT	0.5	[0.4–0.7]	<0.001								



Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial

Sylvie Bonvalot, Alessandro Gronchi, Cécile Le Péchoux, Carol J Swallow, Dirk Strauss, Pierre Meeus, Frits van Coevorden, Stephan Stoldt, Eberhard Stoeckle, Piotr Rutkowski, Marco Rastrelli, Chandrajit P Raut, Daphne Hompes, Antonino De Paoli, Claudia Sangalli, Charles Honoré, Peter Chung, Aisha Miah, Jean Yves Blay, Marco Fiore, Jean-Jacques Stelmes, Angelo P Dei Tos, Elizabeth H Baldini, Saskia Litière, Sandrine Marreaud, Hans Gelderblom, Rick L Haas

EORTC-62092, N=266:

surgery +/- neoadjuvant RT (50,4 Gy)

PE: Abdominal recurrence-free interval

RECIST 1.1: 3% PR, 82% SD, 16% PD, 9% NE

- 1 death in the RT+surgery arm (TRSAE: gastropleural fistula) v. 0 in the surgery arm

	Surgery alone group (n=133)	Preoperative radiotherapy plus surgery group (n=133)
Age (years)	61 (53-67)	61 (52-68)
Sex		
Female	66 (50%)	62 (47%)
Male	67 (50%)	71 (53%)
WHO performance status		
0	100 (75%)	110 (83%)
1	33 (25%)	22 (17%)
2	0	1 (<1%)
Pre-operation biopsy		
Imaging-guided	123 (92%)	119 (89%)
Surgical	10 (8%)	12 (9%)
Missing	0	2 (2%)
Tumour size (mm)	167 (124-210)	160 (111-210)
Histological subtype		
All liposarcoma subtypes	100 (75%)	98 (74%)
Well-differentiated liposarcoma	42 (32%)	46 (35%)
De-differentiated liposarcoma	54 (41%)	51 (38%)
Other liposarcoma	4 (3%)	1 (<1%)
Leiomyosarcoma	22 (17%)	16 (12%)
Other	11 (8%)	18 (14%)
Data missing	0	1 (<1%)
Tumour grade at biopsy		
Low	43 (32%)	44 (33%)
Intermediate	38 (29%)	47 (35%)
High	19 (14%)	12 (9%)
Not evaluable	21 (16%)	17 (13%)
Data missing	12 (9%)	13 (10%)

Post-hoc exploratory analysis in LPS

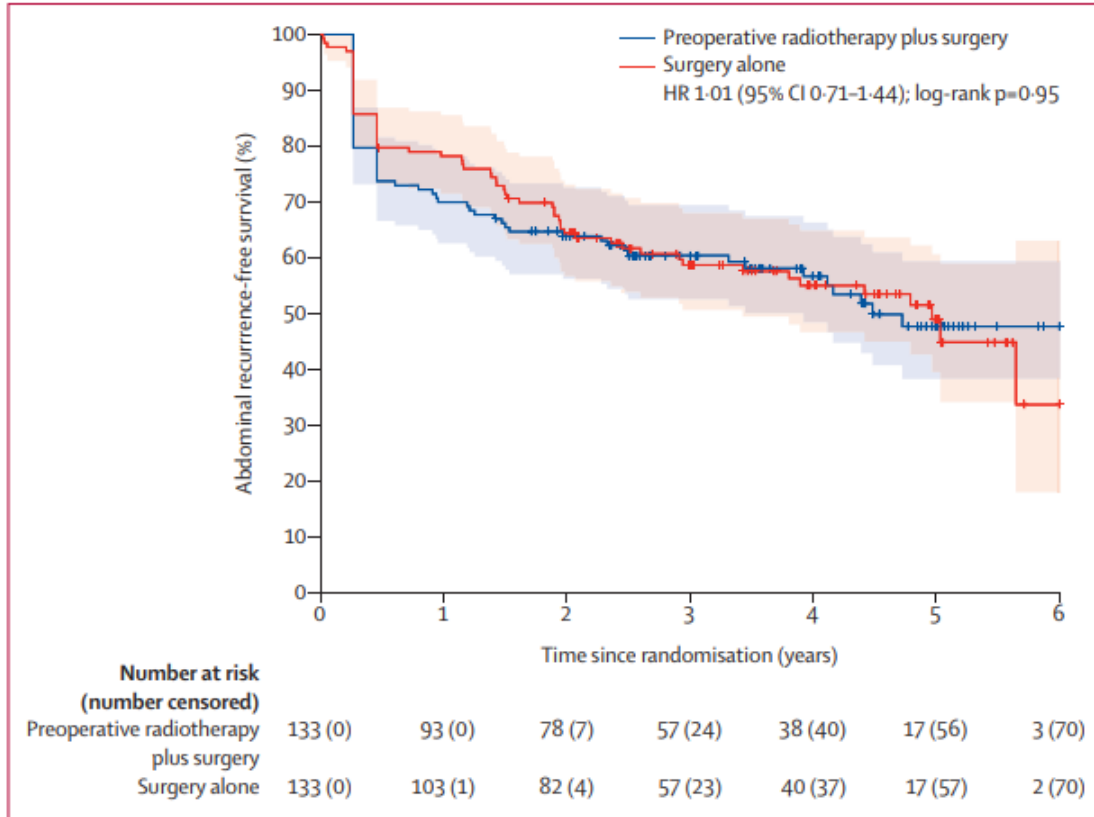


Figure 2: Abdominal recurrence-free survival in all patients
Shaded areas around the lines represent the 95% CI. HR=hazard ratio.

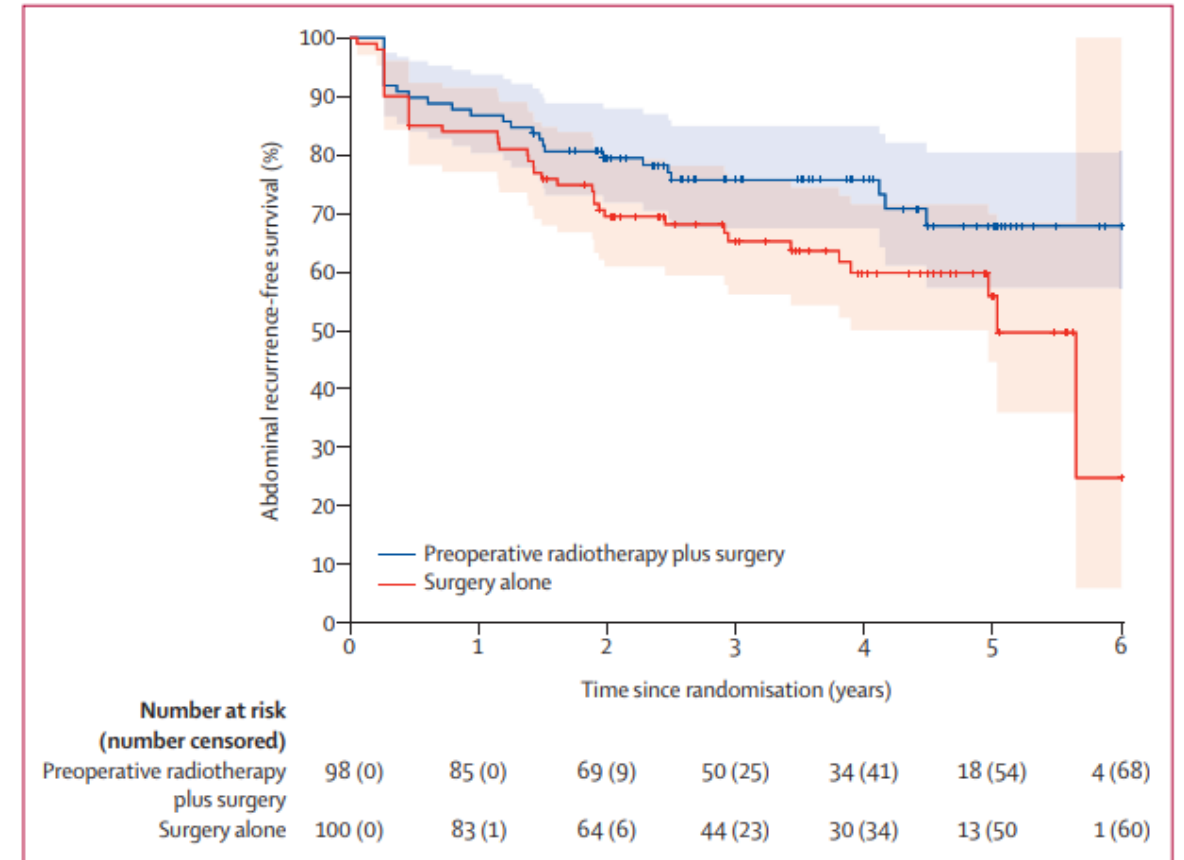


Figure 3: Second sensitivity analysis of abdominal recurrence-free survival in the liposarcoma subgroup
Shaded areas around the lines represent the 95% CI.

- 3y-ARFI 32% in the surgery group and 34.3% in the RT plus surgery group (HR 1.09, p=0.66).
- LPS subgroup: **3y-ARFI** 33.4% in the surgery group and 31.1% in the RT plus surgery group (HR 0.91, 95% CI 0.58–1.42), median **OS** not reached in either group

Pooled analysis of STRASS and STREXIT

- STRASS: n=266
- STREXIT: n=727, 202 after 1:1 propensity score-matching
- No association between RT and DMFS and OS

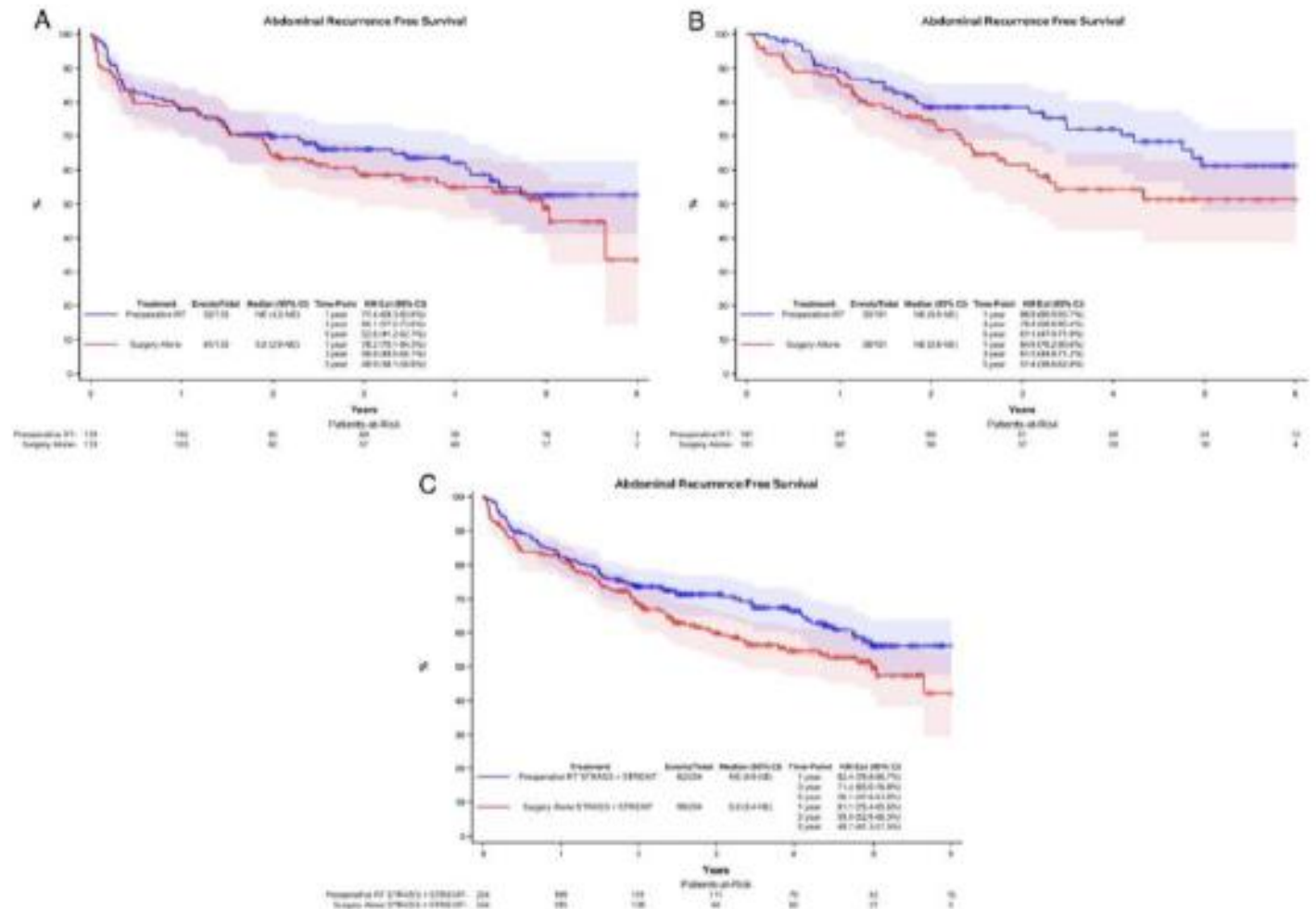
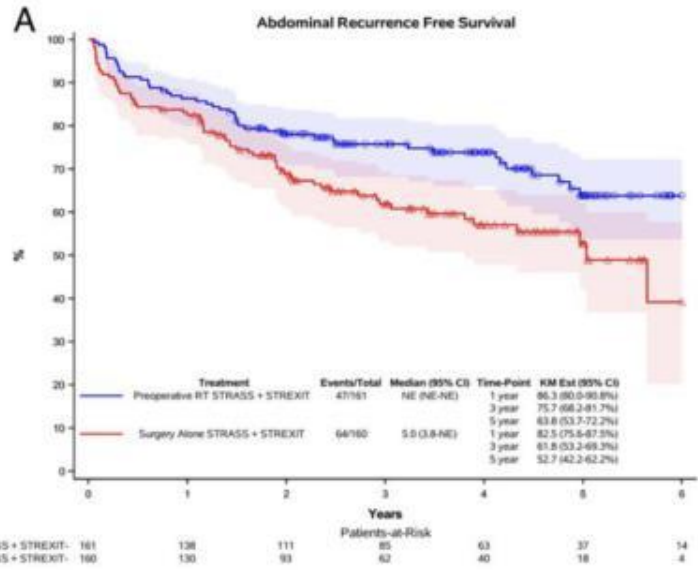


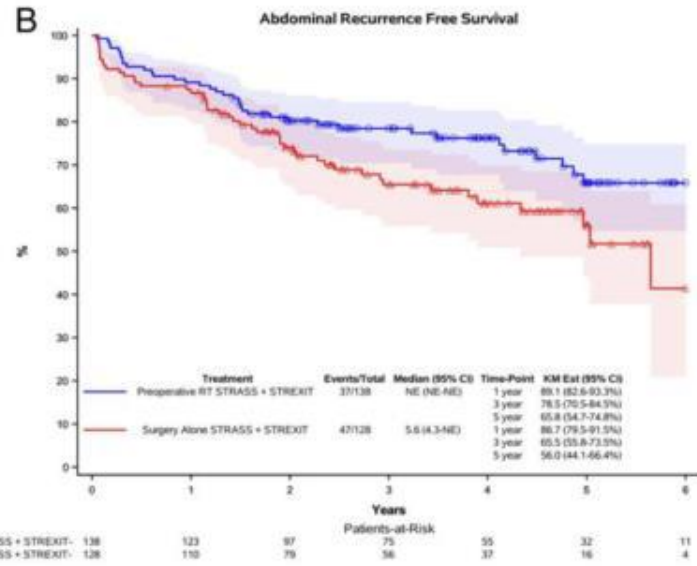
FIGURE 1. Abdominal recurrence-free survival curves according to treatment (blue: preoperative radiotherapy + surgery; red: surgery alone) in STRASS (A), STREXIT after 1:1 propensity score-matching (B), and pooled cohort (C).

LPS
HR 0.61

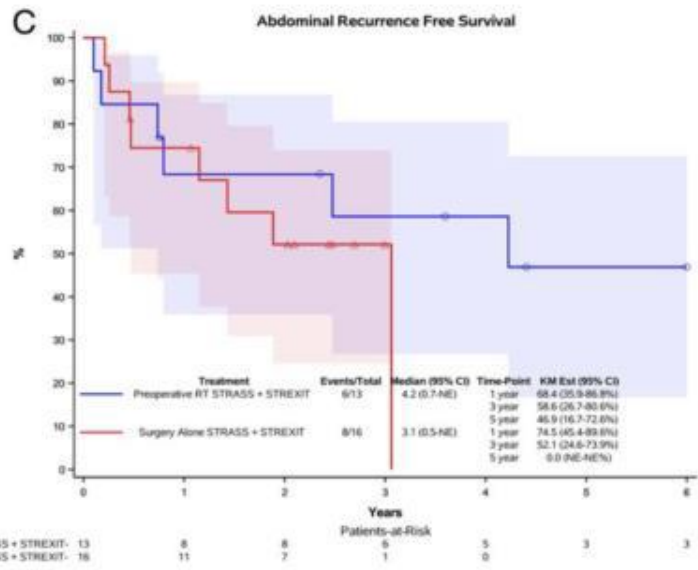


WDLPS and
G1-2 DDLPS

HR 0.63
5y-ARFS: 65.8%
v. 56.0%



G3 DDLPS
HR 0.68



LMS
HR 0.99

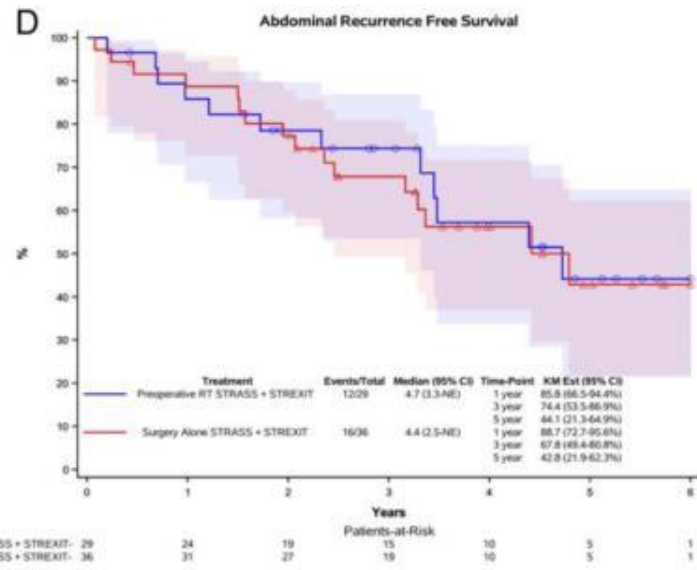
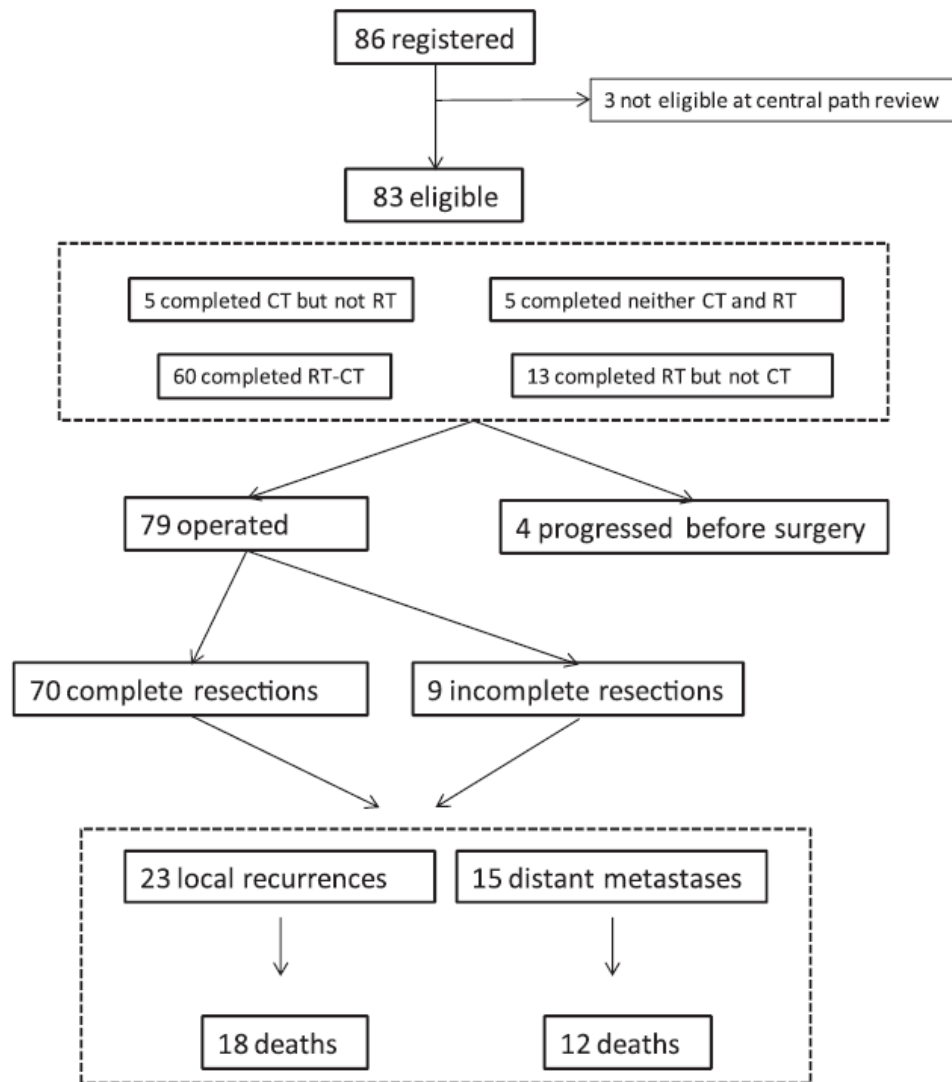


FIGURE 2. Abdominal recurrence-free survival curves in the pooled cohort subgroup analyses according to treatment (blue: preoperative radiotherapy + surgery; red: surgery alone). A, Patients with liposarcoma. B, Patients with G1-2 dedifferentiated liposarcoma and well-differentiated liposarcoma. C, Patients with G3 dedifferentiated liposarcoma. D, Patients with leiomyosarcoma.

Neoadjuvant concurrent chemo/RT

Preoperative chemo-radiation therapy for localised retroperitoneal sarcoma: A phase I–II study from the ISG



Histological subtype

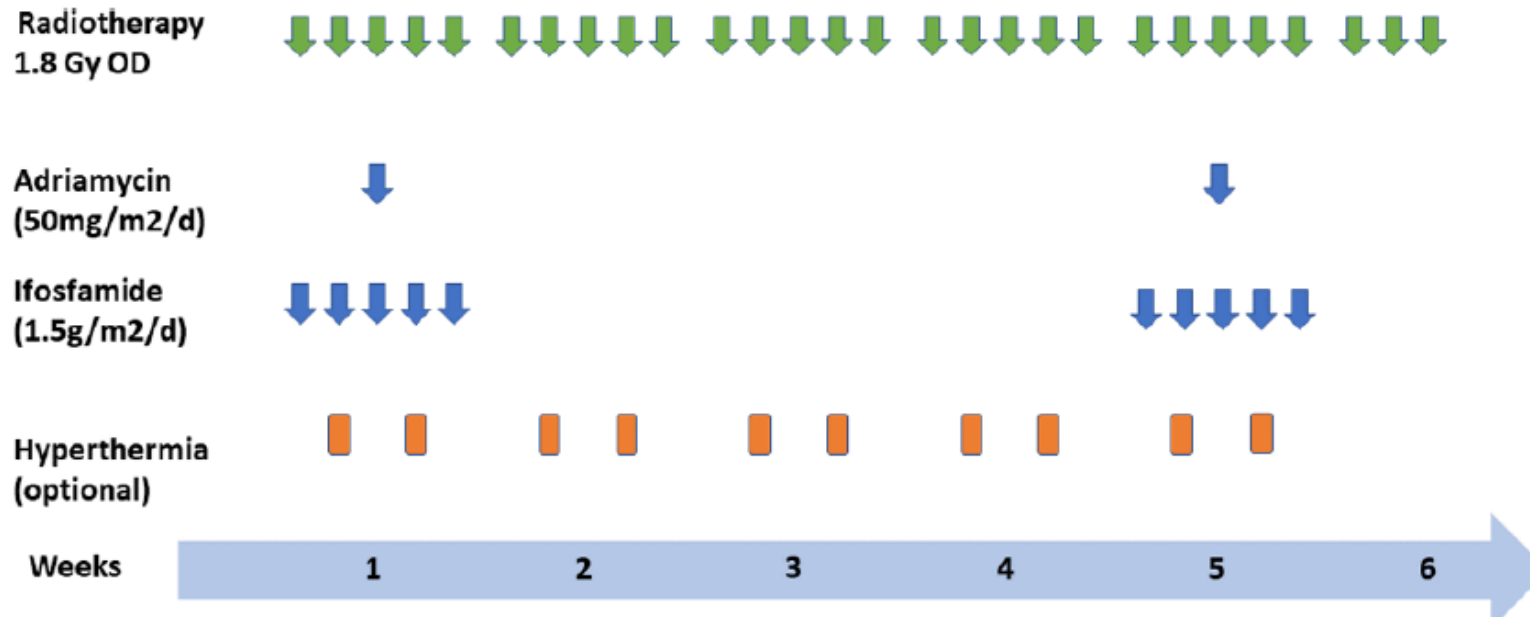
Well-differentiated liposarcomas	19	(22.9)
Dedifferentiated liposarcomas	26	(31.3)
Leiomyosarcoma	14	(16.9)
Undifferentiated sarcoma NOS	8	(9.6)
Other	16	(19.3)

- 2003-2010
- 63 primary RPS, 20 recurrent
- x3 high-dose Ifo (14 g/m²) + RT from C2
- 3y-RFS=0.56, 5y-RFS=0.44
- 5y-OS=0.59

Neoadjuvant concurrent chemoradiotherapy with and without hyperthermia in retroperitoneal sarcomas: feasibility, efficacy, toxicity, and long-term outcome

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- Retrospective, German single-institution
- N=27 G2-G3 RPS (12 DDLPS, 10 LMS, 5 other)
- 92% completed treatment and underwent surgery
- N=15 +hyperthermia
- 5y-ARFS 74.6%, 10y-ARFS 66.3%
- 5y-DMFS 67.2%, 10y-DMFS 59.7%
- 5y-OS 60.3%, 10y-OS 60.3%
- signal that combined chemoradiation might be superior to RT alone?

Conclusions

- Complete surgical resection remains the cornerstone of therapy for RPS
- Neoadjuvant chemo could be used in case of borderline resectable RPS.
- STRASS-2 trial will answer the question of neoadjuvant chemo in resectable high-risk RPS
- Neoadjuvant RT can be discussed in case of G1-G2 LPS

Thank you very much for your attention

