

Improving the outcome of Retroperitoneal Sarcomas

Optimal surgical control and minimal
surgical morbidity



Mr Dirk Strauss
Consultant Surgeon

The ROYAL MARSDEN
NHS Foundation Trust



Introduction

- Background
- RMH experience
- Potential strategies to improve outcome
 - Radiotherapy
 - High-volume centres
 - Importance of microscopic margins in RPS
 - Optimal extent of surgical resection
- Conclusion



Background

- Complete surgical resection offers the only opportunity for cure in patients with primary retroperitoneal sarcomas (RPS)
- Surgery is often a major undertaking
 - no effective chemotherapy exists to cure RPS
 - radiotherapy is seldom possible due to toxicities to adjacent structures

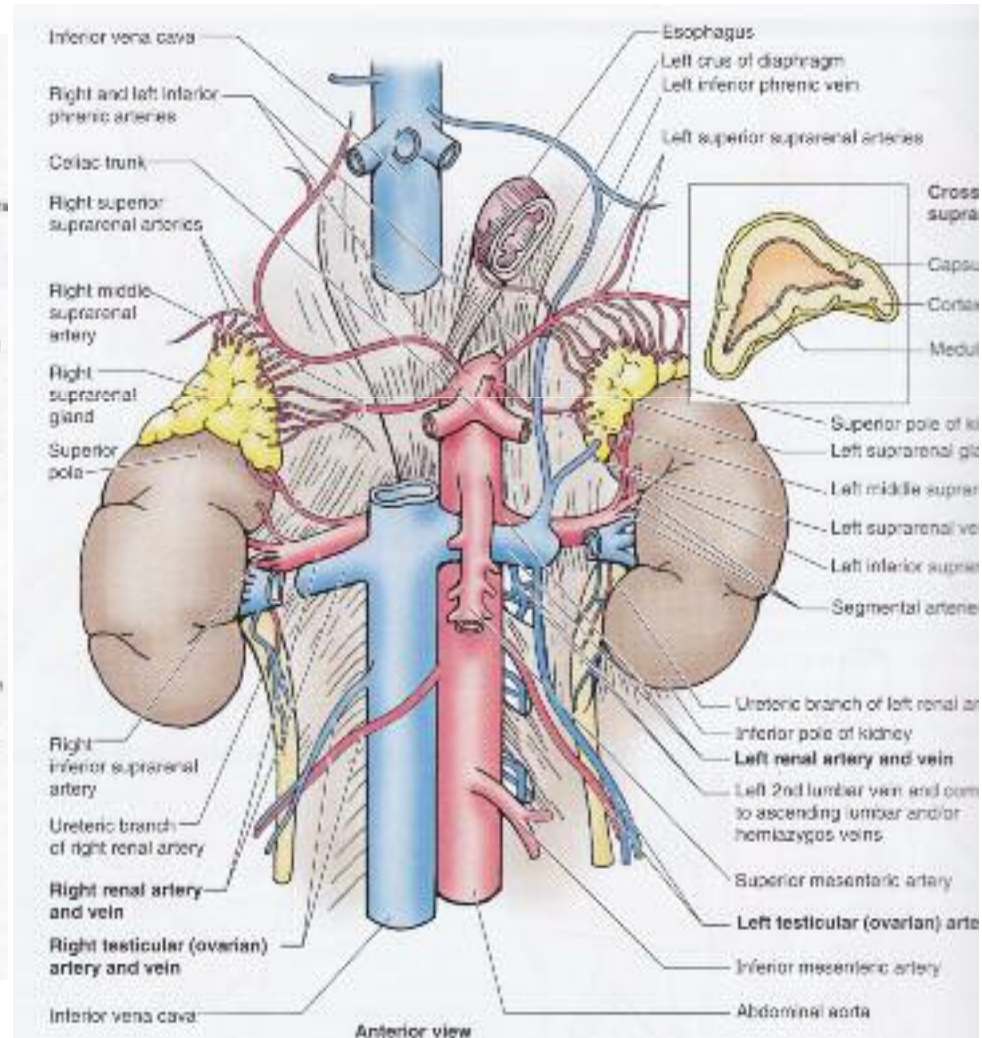
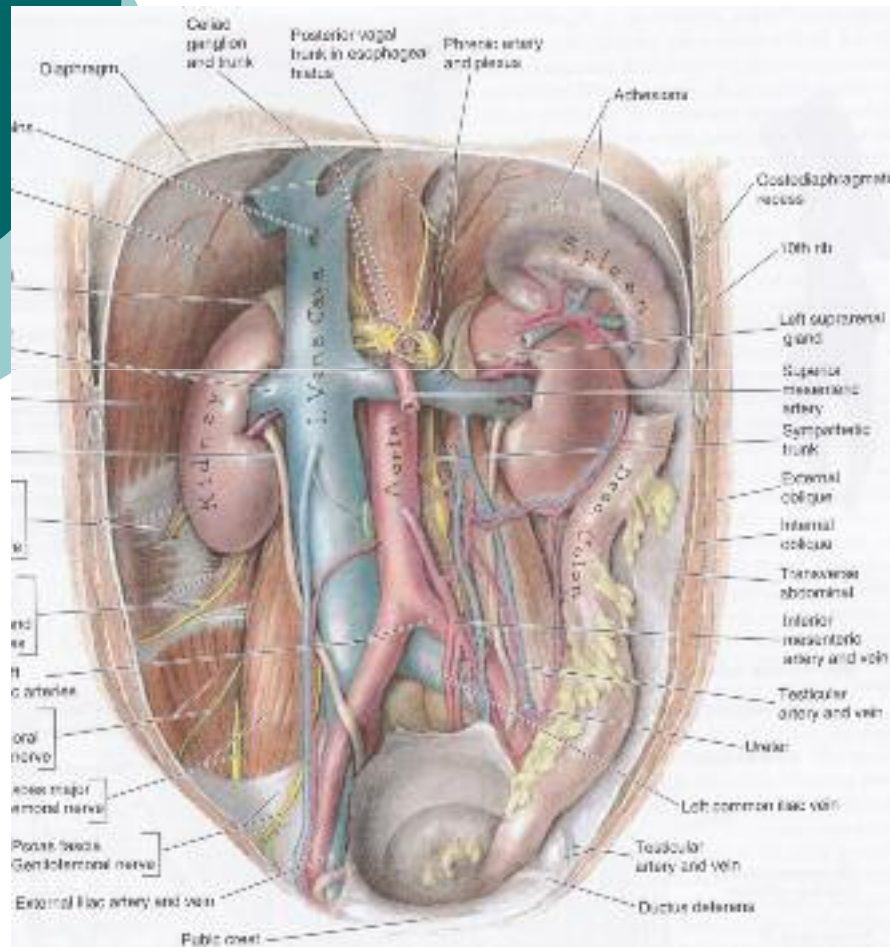


Background

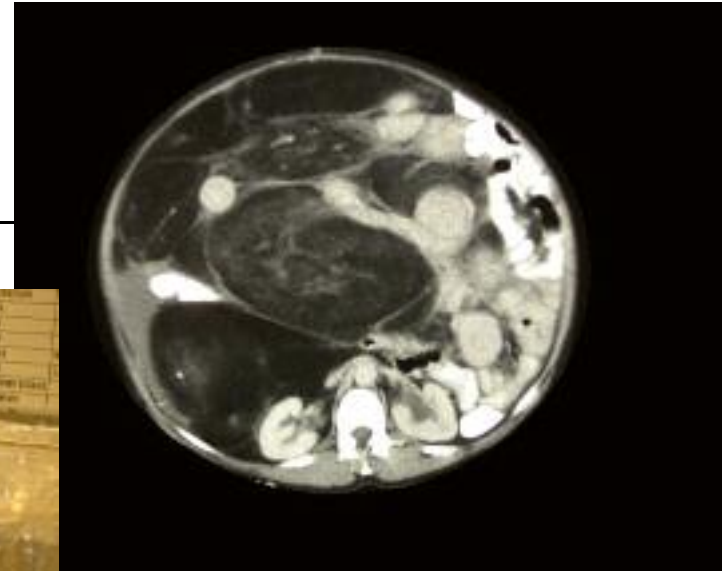
Surgery for RPS constitute a therapeutic challenge

- relative late presentation
- anatomical location
 - close relationship with multiple vital structures
 - anatomically complex retroperitoneal space
- close relationship to vital structures impacts on the ability to perform a radical wide resection

Retroperitoneal space



Record of all RPS



Surgery for RPS



The proud team!





Failure of local control

- Local recurrence is the main cause of medium and long term failure, ranging from 40 – 80%.
- 75% of RPS-related deaths result from uncontrolled local recurrence



Royal Marsden Hospital experience

- Primary retroperitoneal sarcomas
- experience of two surgeons within one centre
- a consistent operative approach
 - obtaining complete clearance of all macroscopic disease,
 - resection of adjacent organs or vascular structures when macroscopically involved by tumour,
 - but preservation of macroscopically uninvolved organs even if they were closely apposed to the surface of the tumour



Methods

- RMH prospectively maintained database for all patients with soft tissue tumours treated since 1990
- Patient factors, operative outcomes and tumour variables were correlated with the local recurrence and disease-specific survival
- Multidisciplinary team



Operative approach

- Organs were resected to obtain macroscopic clear margins when the contiguous organ appeared clinically involved or to facilitate safe dissection around the tumour.
- Clinically uninvolved but adjacent organs were not an indication for resection.



Methods

- Primary endpoints
 - local recurrence and disease-specific survival
- Follow-up program consists of review at 3-month intervals for 1 year, review at 6-month intervals for the next four years and then annually.



Results

Total	n = 200
Male:female	114:86
Age	Median 56 years (18 – 89)
Median follow-up (months)	29 months (range 0 – 198 months)



Results

Tumour size (diameter)	median - 27cm range 6 – 60cm
Size distribution	n = 200
6 – 9.9cm	4
10 – 19.9cm	51
20 – 39.9cm	108
> 40cm	37
Tumour weight (g)	median – 4000g range 32 – 25 000g
Tumour grade	n = 200 Grade 1 - 93 Grade 2 - 81 Grade 3 - 26

Record primary RPS




Weight of Specimen

24.5

GRAND TOTAL = 25.515 kg

	WT
TUMOR	30.1
PLATES	25.3
DISSECTOR	32 1/2
LIFTER	35
BROWN	28 kg
K.	31 kg
Rodentek	30
Phil	27
Zany	28.5
Lee	23.5



55lb tumour missed for decade

By Nigel Hawkes
Health Editor

FOR nearly ten years Trevor Smithson was told by doctors that he was dangerously obese and had only himself to blame for his constant pain, chronic backache and circulation problems.

"I think everyone just took one look at me and thought I drank 15 pints a day," said Mr Smithson, a 53-year-old aeronautical engineer.

Every few months he would visit the Royal Berkshire Hospital in Reading, and every time he was told he was fat, and sent away to lose weight.

It was not until he finally went for a consultation at the Royal Marsden Hospital in London that doctors realised the truth: Mr Smith had developed a 25kg (55lb) malignant tumour over a decade.

By the time it was removed last year, its size had displaced his other internal organs. He lost a kidney and a section of his colon in the operation, needing breathing support as his lungs recovered from being crushed by the tumour.

Now Mr Smithson, who has been left partially disabled by the ordeal, has referred his complaint to the Healthcare Commission. "[It is] incomprehensible that the collective wisdom and equipment of Royal Berkshire Hospital could somehow manage not to find a 25kg malignant tumour over a period approximating to a decade," he said.

Mr Smithson, 53, says that he complained about a gross-

ly distorted abdomen and accompanying pain in 1994. He was referred to the hospital by his GP, but when he was seen there he was told he was fat.

When he finally reached the Royal Marsden, he says, the first reaction of Meirion Thomas, his surgeon, was: "So you've not been to see your doctor for years and years, have you?" He had to explain that he had been seeing doctors at regular intervals, with no satisfaction.

Mr Thomas removed what

are described in Mr Smithson's discharge notes as "a truly immense intra-abdominal liposarcoma". These are slow-growing malignant tumours that develop in fat tissue, and are often found in the abdominal cavity.

They are soft and can be difficult to diagnose, but Mr Smithson says that he had a range of symptoms that ought to have alerted doctors, including backache, circulation problems in his scrotum and a colon so displaced that it could be felt through the abdominal wall.

He also had excessive body weight while not having any symptoms of obesity anywhere else in his body. "I was constantly shopping for ever-increasing sizes of clothes," he said. "I'm a tall man and when I was also that heavy I wore out my shoes very quickly."

"I went through a difficult time career-wise. I was an aeronautical engineer but I couldn't get a job. Once they had decided I was just obese they didn't take any further action."

Yesterday the hospital said

that while they could not discuss individual cases, this particular type of tumour could be difficult to diagnose, and that it might take years to discover.

"If one looked for one thing and didn't have enough information to look for anything else, one might not do tests," a spokeswoman said, making clear that she was talking in general terms and not specifically about Mr Smithson.

"We take complaints very seriously and investigate them thoroughly."



Before: tumour undiagnosed



After: recovering at home

It pays to read the small print

By Dr Thomas Stuttford

MEDICAL students are taught two similar axioms that are supposed to help them to reach a diagnosis. One is that common diseases occur; the other is that if someone says there is a bird on the lawn, it is more likely to be a house sparrow than a Eurasian siskin.

Many patients have died and even more been left permanently harmed because doctors, remembering this teaching, have not thought beyond the obvious. Mr Smithson had a liposarcoma, a disease that does not commonly occur.

Furthermore, lipomas or liposarcomas do not show up

well initially on X-ray. Although liposarcomas are rare, the body develops their benign counterpart, lipomas, relatively commonly. Lipomas that are especially likely to become liposarcomas and malignant are those that develop in the stomach or on a lipoma on the thigh. Any lipoma growing more quickly than usual needs removal and microscopic examination.

The lesson to be learnt from this case is that, although Eurasian siskins are rare in southern England, they are found occasionally.

So too are those diseases mentioned in the small print in medical textbooks.



Tumour subtype

Liposarcoma (LPS)	148
- Well-differentiated LPS	87
- Dedifferentiated LPS	55
- Myxoid LPS	3
- Pleomorphic LPS	3
Leiomyosarcoma	27
Solitary fibrous tumour	11
Synovial sarcoma	3
Fibrosarcoma	2
Pleomorphic sarcoma	2
Spindle cell sarcoma NOS	2
Pleomorphic rhabdomyosarcoma	1
Undifferentiated round cell sarcoma	1
Malignant PNST	1
Epithelioid smooth muscle tumour	1
Desmoplastic small round cell tumour	1



Operative outcomes

ITU stay - median - range	1 day 0 – 67 days
Blood loss - median - range	1500ml 100ml – 16litres
Postoperative Mortality = 3% (6/200 patients)	
Postoperative Morbidity = 12% (24/200 patients)	



Results – macroscopic clearance

- Macroscopic clearance (R0/R1) = 85%
(170/200)
- Incomplete resection (R2) = 15%
(30/200)



Resection of adjacent organs

Required in 126 patients (63%)	
Kidney	71
Colon	44
Spleen	28
Distal pancreas	17
Partial stomach	4
IVC	4
Partial bladder	3
Small bowel	5
Other*	17
Abdominal wall + mesh reconstruction	1
AAA repair	1

* Iliac artery(1), iliac vein(2), spermatic cord and testis(3), diaphragm(3), duodenum(2), ovary(2), uterus(2), gallbladder(2).



Outcome – follow up

- 75/200 patients (38%) developed local recurrence
- End of the study
 - 141 of the 200 patients were alive at last follow-up,
 - 6 patients died during the postoperative period,
 - 45 patients died due to sarcoma-related causes
 - 8 patients died due to unrelated causes.

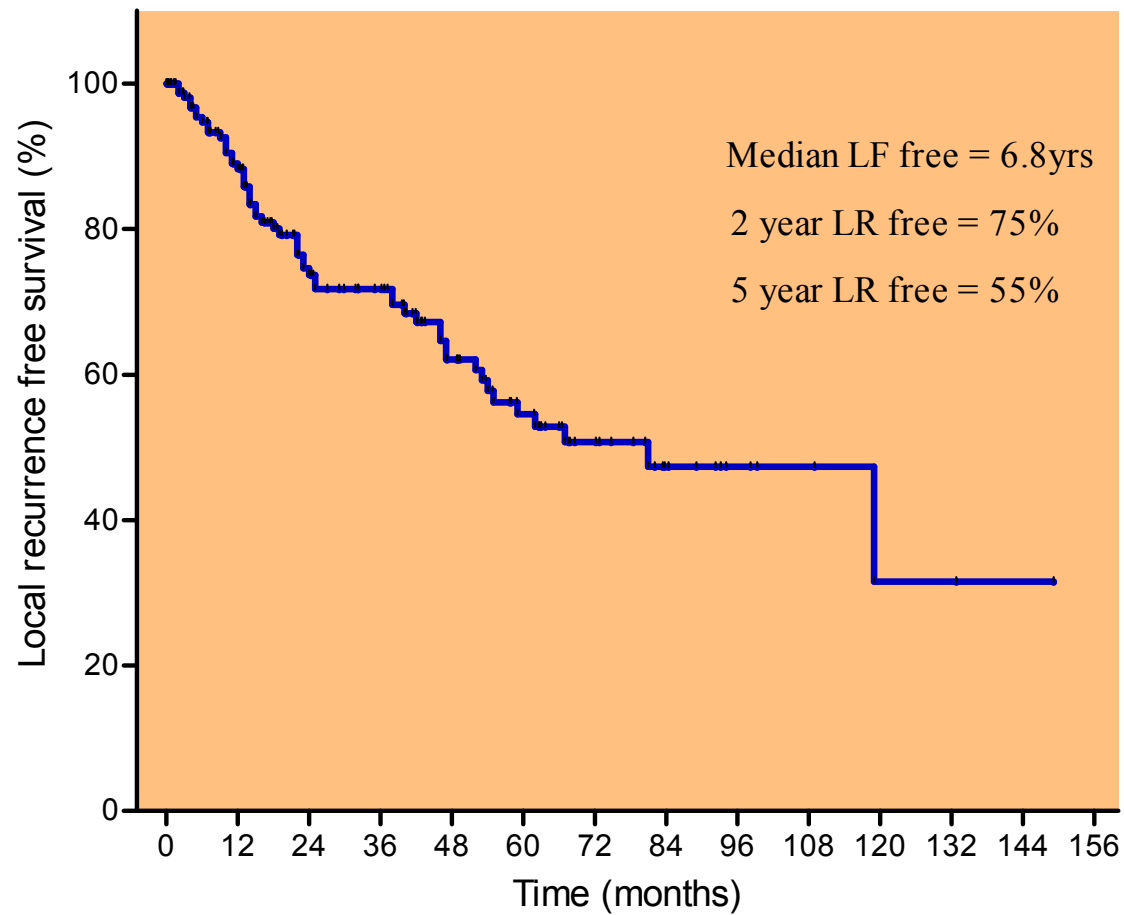


Outcome – LR free survival

- Median local recurrence-free survival = 3.8yrs (200 patients)
- Macroscopic complete resection, median local recurrence-free survival = 6.8 years (170/200 patients)
- 2-year local recurrence-free survival = 75%
- 5-year local recurrence-free survival = 55%

Outcome – LR free survival

Overall local recurrence-free survival



Local recurrence-free survival

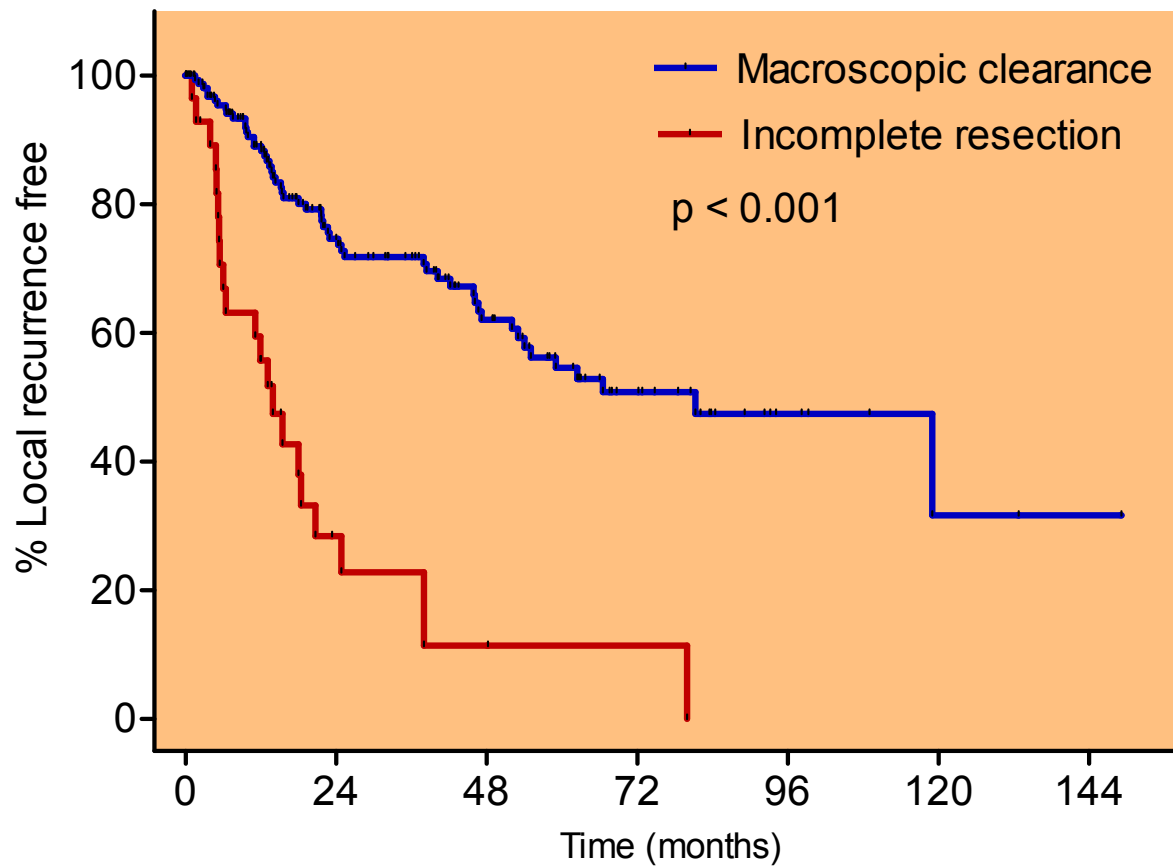
		Univariate analysis		Multivariate analysis	
		Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Tumour grade	1	1		1	
	2	3.6 (2.2, 5.8)	<0.001	3.4 (2.1, 5.5)	<0.001
	3	5.1 (2.7, 9.8)	<0.001	4.7 (2.4, 9.0)	<0.001
Macroscopic clearance	Yes	1		1	
	No	2.0 (1.6, 2.5)	<0.001	3.6 (2.3, 5.9)	<0.001
Age (cont)	1-yr increase	1.0 (0.999, 1.03)	0.059		
Age (categorical)	<=median(57)	1			
	> median(57)	1.2 (0.8, 1.8)	0.387		
Tumour size	<= 30cm	1			
	>30 cm	0.7 (0.5, 1.2)	0.185		
Tumour weight	<=4kg	1			
	> 4kg	0.9 (0.6, 1.4)	0.702		

Local recurrence-free survival

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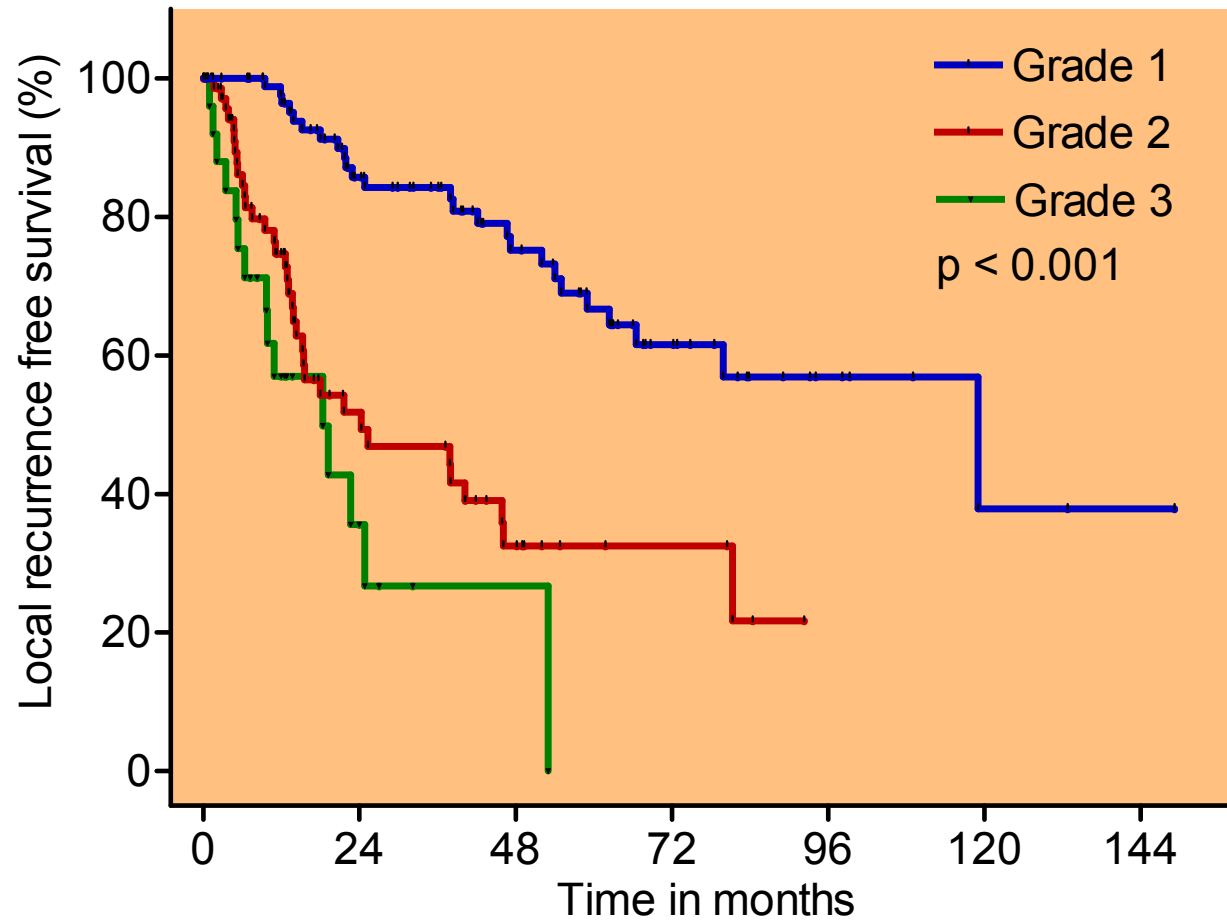
Local recurrence-free survival

Local recurrence free survival comparing complete macroscopic clearance against incomplete resection



Local recurrence-free survival

Local recurrence free survival according to grade



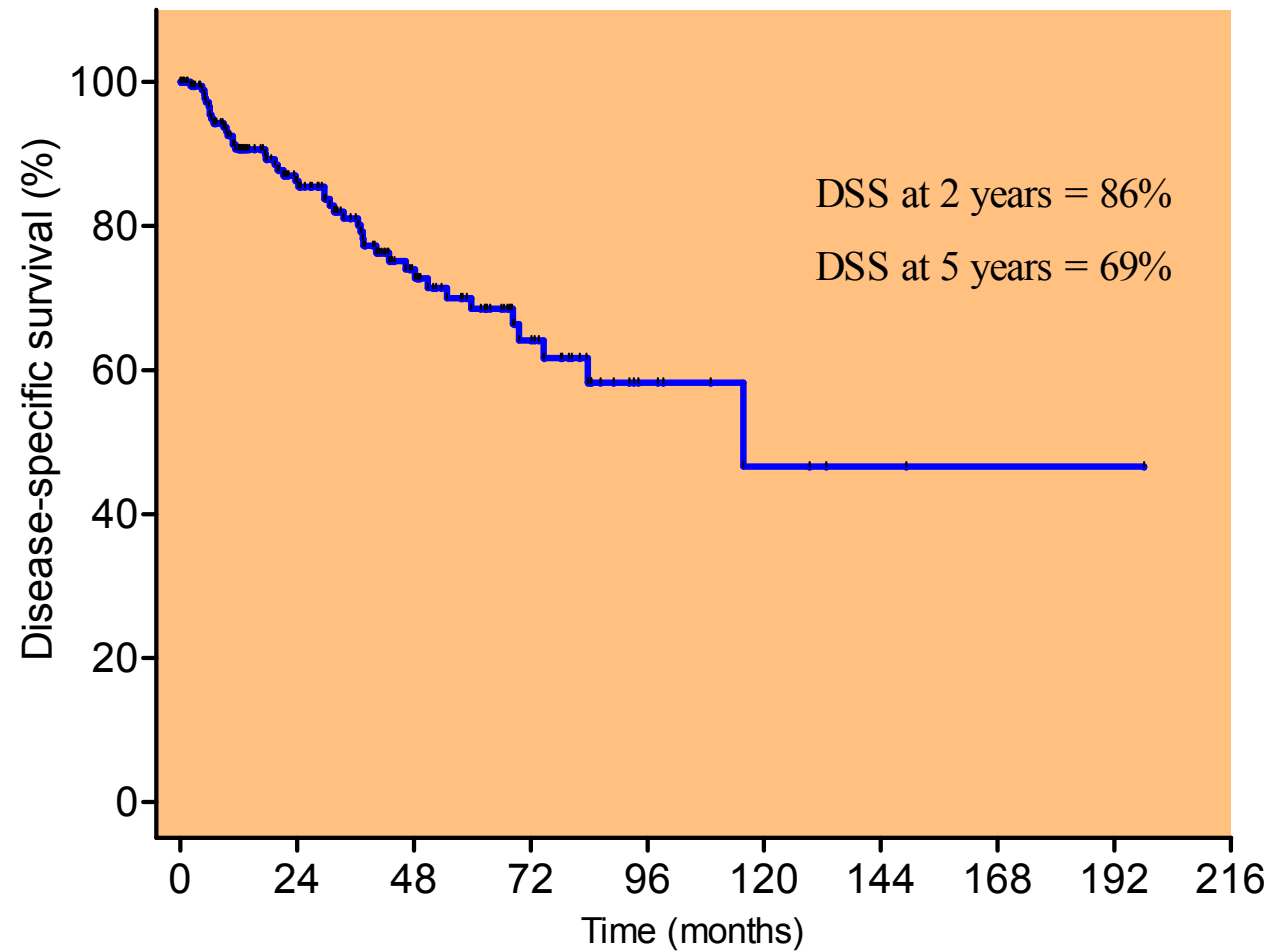


Disease-specific survival

- Median disease-specific survival (DSS) was 115 months (9.6yrs)
- Disease-specific survival at 2 years = 86%
- Disease-specific survival at 5 years = 69%

Disease-specific survival

Disease-specific survival



Disease-specific survival

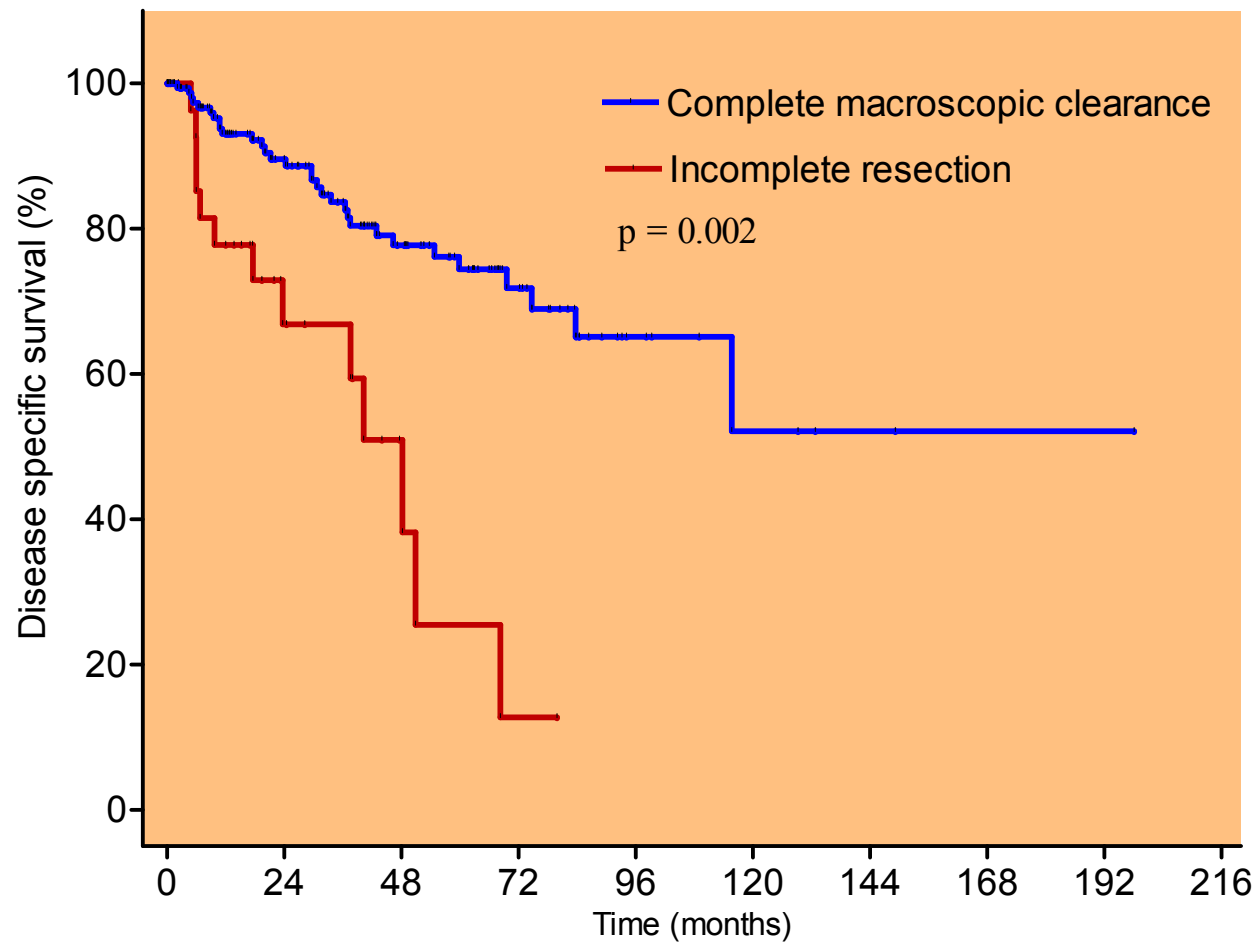
		Univariate analysis		Multivariate analysis	
		Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Grade	1	1	<0.001	1	<0.001
	2	7.4 (3.3, 16.6)	<0.001	7.6 (3.3, 17.5)	<0.001
	3	15.8 (6.1, 40.8)		17.3 (6.5, 46.3)	
Macroscopic clearance	Yes	1	<0.001	1	0.002
	No	1.9 (1.4, 2.7)		2.9 (1.5, 5.8)	
Pathology	ALT	1	<0.001		
	Non-ALT LPS	6.0 (2.7, 13.3)	<0.001		
	Other	4.4 (1.9, 10.1)			
Age (cont)	1-yr increase	1.0 (0.99, 1.04)	0.325		
Age (categorical)	<=median(57)	1	0.630		
	> median(57)	1.2 (0.6, 2.1)			
Tumour size	<= 30cm	1	0.048	1	0.052
	>30 cm	0.5 (0.3, 1.0)		0.5 (0.2, 1.0)	
Tumour weight	<=4kg	1	0.705		
	> 4kg	1.1 (0.6, 2.2)			

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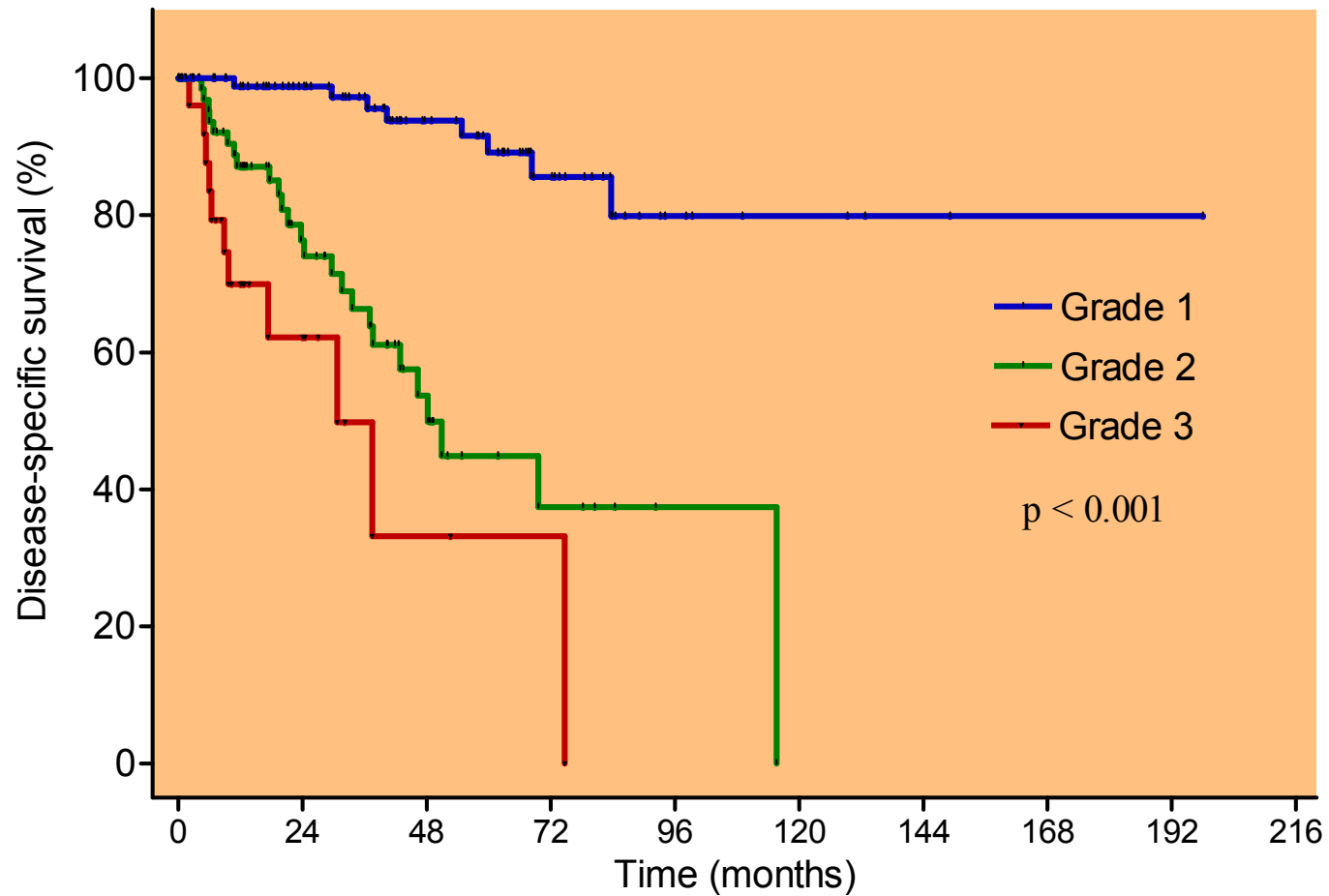
Disease-specific survival

Disease-specific survival relating to macroscopic clearance



Disease-specific survival

Disease-specific survival according to tumour grade





Systemic metastases

- Seventeen patients (8.5%) were diagnosed with systemic metastasis during the follow-up period after surgery.
- Metastatic disease occurred exclusively in patients with grade 2 and 3 tumours.
- All systemic metastasis presented within 33.6 months after surgery.



Adjuvant treatment

- 18 (9%) patients received radiotherapy
- 25 (13%) patients received chemotherapy



Findings

- Complete macroscopic excision should be the goal of surgical resection.
- The ability to completely resect a RPS combined with the tumour grade are the most important predictor of local recurrence and disease-specific survival.



Role of microscopic margins

- The evaluation of microscopic margins is problematic
 - Large tumours, extensive tumour surface area making it hard to reliably assess all microscopic margins.
 - The ability to accurately determine clear microscopic margins will closely related to the methodology of pathological sampling.
 - The microscopic margins may also be disturbed by tumour handling and retraction artefacts after resection and do not necessarily indicate microscopic residual disease.



Microscopic margins - evidence

ORIGINAL PAPERS AND DISCUSSIONS

Histologic Subtype and Margin of Resection Predict Pattern of Recurrence and Survival for Retroperitoneal Liposarcoma

Samuel Singer, MD, Cristina R. Antonescu, MD,† Elyn Riedel, MA,‡ and Murray F. Brennan, MD**

Objective: The aim of this study was to determine the pattern of recurrence and prognostic significance of histologic subtype in a large series of patients with primary retroperitoneal liposarcoma.

Summary Background Data: Classification of liposarcoma into subtypes, based on morphologic features and cytogenetic aberrations, is now widely accepted. Previous studies have shown that high histologic grade and incomplete gross resection are the most important prognostic factors for survival in patients with retroperitoneal

Conclusions: The histologic subtype and margin of resection are prognostic for survival in primary retroperitoneal liposarcoma. Dedifferentiated histologic subtype and the need for contiguous organ resection (excluding nephrectomy) was associated with an increase risk of local and distant recurrence. Nephrectomy may be needed to achieve complete resection, but has no measurable influence on disease specific survival.

(Ann Surg 2003;238: 358–371)

Microscopic margins - evidence

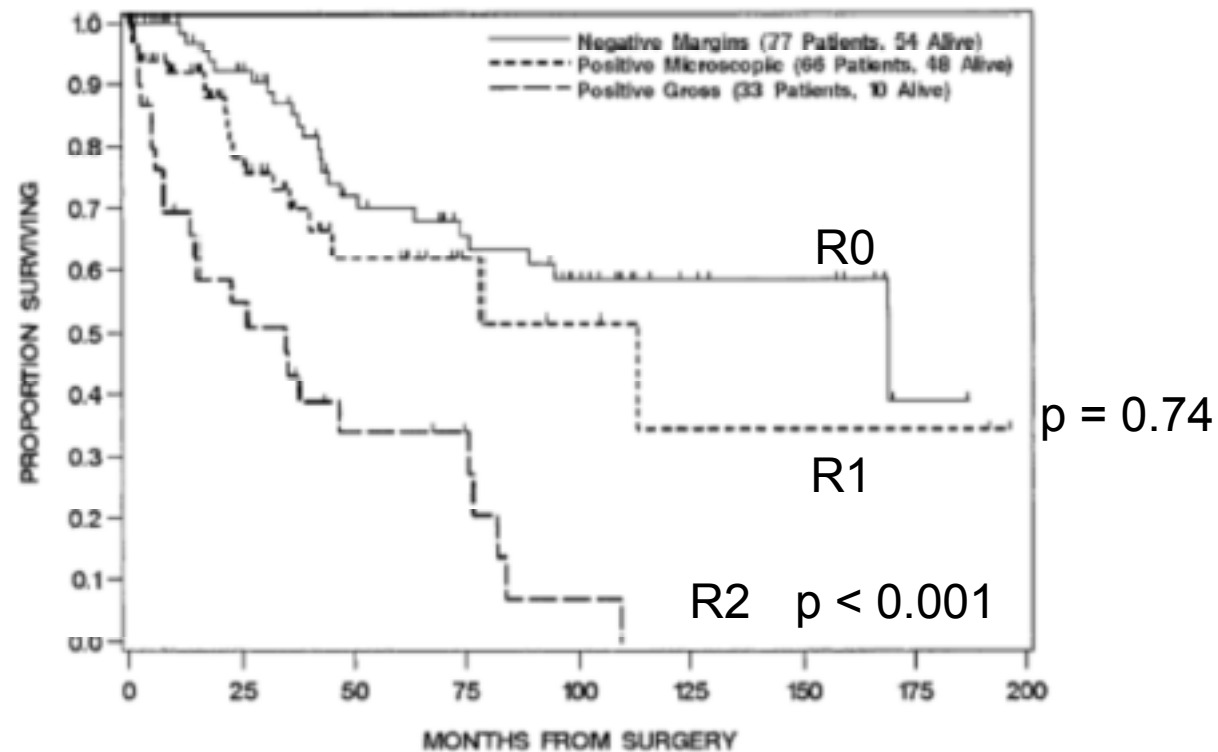


FIGURE 3. DSS by margin status.



Microscopic margins - evidence

ORIGINAL ARTICLES

Subtype Specific Prognostic Nomogram for Patients With Primary Liposarcoma of the Retroperitoneum, Extremity, or Trunk

Kimberly Moore Dalal, MD, Michael W. Kattan, PhD,† Cristina R. Antonescu, MD,‡
Murray F. Brennan, MD,* and Samuel Singer, MD**

Objective: To determine the prognostic significance of histologic subtype in a large series of patients with primary liposarcoma (LS) and to construct a LS-specific postoperative nomogram for disease-specific survival (DSS).

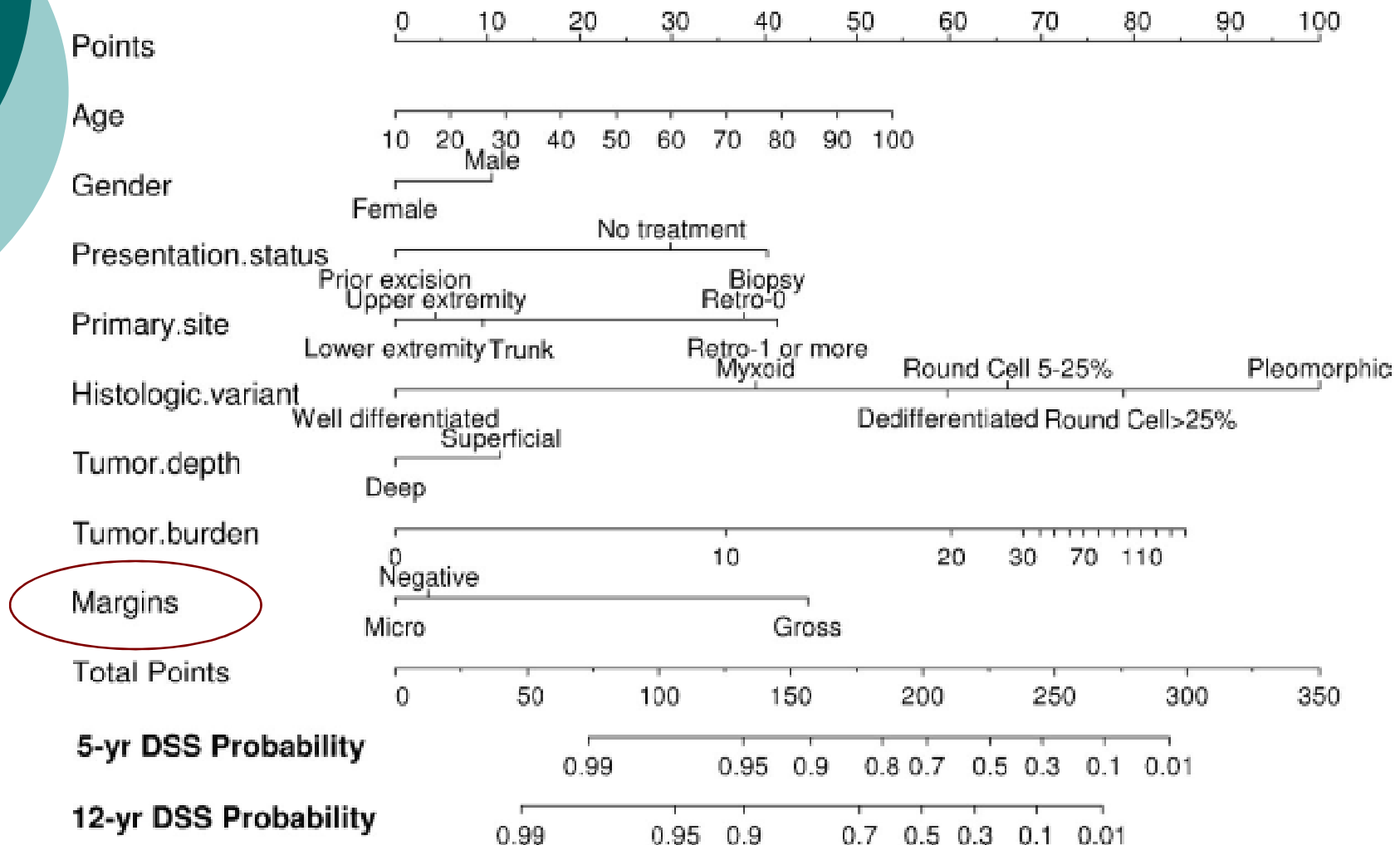
Summary Background Data: Nomograms, used to define and predict outcome following operative intervention, may contain variables not conventionally used in standard staging systems. A 12-year DSS postoperative nomogram for all sarcomas has already been established.

gram. DSS nomograms aid in more accurate counseling of patients, identification of patients appropriate for adjuvant therapy, and stratification of patients for clinical trials and molecular analysis.

(Ann Surg 2006;244: 381–391)

■ liposarcoma (LS) is the most common soft tissue sarcoma

Microscopic margins - evidence





Microscopic margins - evidence

“Inspection of the margin of resection axis reveals that a grossly positive margin is associated with a significantly worse prognosis compared with negative or microscopically positive margins. Incomplete resection is a particularly important prognostic factor in primary retroperitoneal LS with a hazard ratio of 3.8 for DSS.”

“In extremity LS, margins may make a difference in outcome, but in retroperitoneal LS, complete gross resection is the dominant factor.”



1. Potential strategies to improve local control

- Radiotherapy to assist in obtaining local control
 - no RCT evidence exist
 - tumours are large at presentation adjacent to radiosensitive structures with low radiation tolerance
 - heterogeneous group of pathologies
 - pre/intra/postoperative



2. Potential strategies to improve local control

ORIGINAL ARTICLES

Should Soft Tissue Sarcomas Be Treated at
High-volume Centers?
An Analysis of 4205 Patients

*Juan C. Gutierrez, MD, Eduardo A. Perez, MD, Frederick L. Moffat, MD, Alan S. Livingstone, MD,
Dido Franceschi, MD, and Leonidas G. Koniaris, MD*

Conclusions: STS patients treated at HVC have significantly better survival and functional outcomes. Patients with either large (>10 cm), high-grade or truncal/retroperitoneal tumors should be treated exclusively at a high-volume center.

(Ann Surg 2007;245: 952–958)

High-volume compared to low-volume centres

TABLE 3. Outcomes for Patients Following Surgical Resection for Soft Tissue Sarcoma According to Volume of Medical Facility

Outcome	Low-Volume Center (n = 2865; 68.1%)	High-Volume Center (n = 1340; 31.9%)	<i>P</i> *
30-day mortality (%)	1.5	0.7	0.028
90-day mortality (%)	3.6	1.6	<0.001
Amputation rate (%)	13.8	9.4	0.048

**P* value by χ^2 test for association between volume and outcomes.



3. Potential strategies to improve local control

- Limb sarcomas – goal of surgery is to resect a tumour, with a rim of health tissue around the tumour, or resection of muscle compartment
- Role of liberal visceral en bloc resection
 - attempt to include an envelope of normal tissue around the tumour to minimise the marginality of the resection in the hope of improving outcome



Potential strategies to improve local control

- The concept of 'compartmentalisation' that applies to limb sarcomas is difficult to extrapolate directly to retroperitoneal sarcomas



Potential strategies to improve local control

- certain structure can be liberally resected
 - the colon, pancreas, spleen and psoas
- close relationship between the tumour and
 - major vessels (aorta, IVC, portal vein, SMA),
 - visceral organs (duodenum, pancreas, liver),
 - axial skeleton (spinal vertebrae),
 - pelvic bones, muscles (abdominal wall) and vital neural structures (femoral nerve roots)



Potential strategies to improve local control

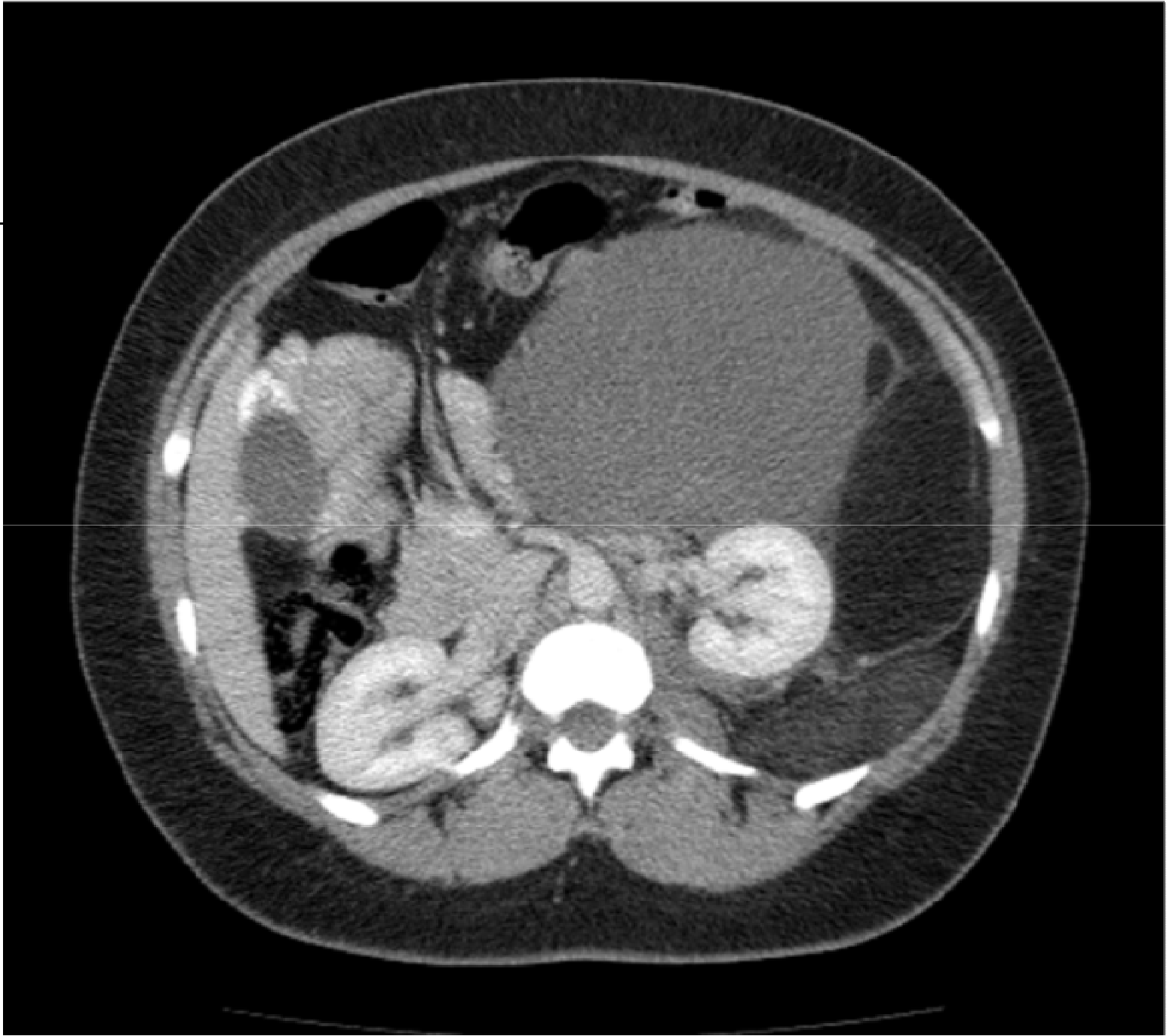
The probability of local recurrence will be determined by your most limited margin, and this unfortunately often relates to surrounding vital organs.

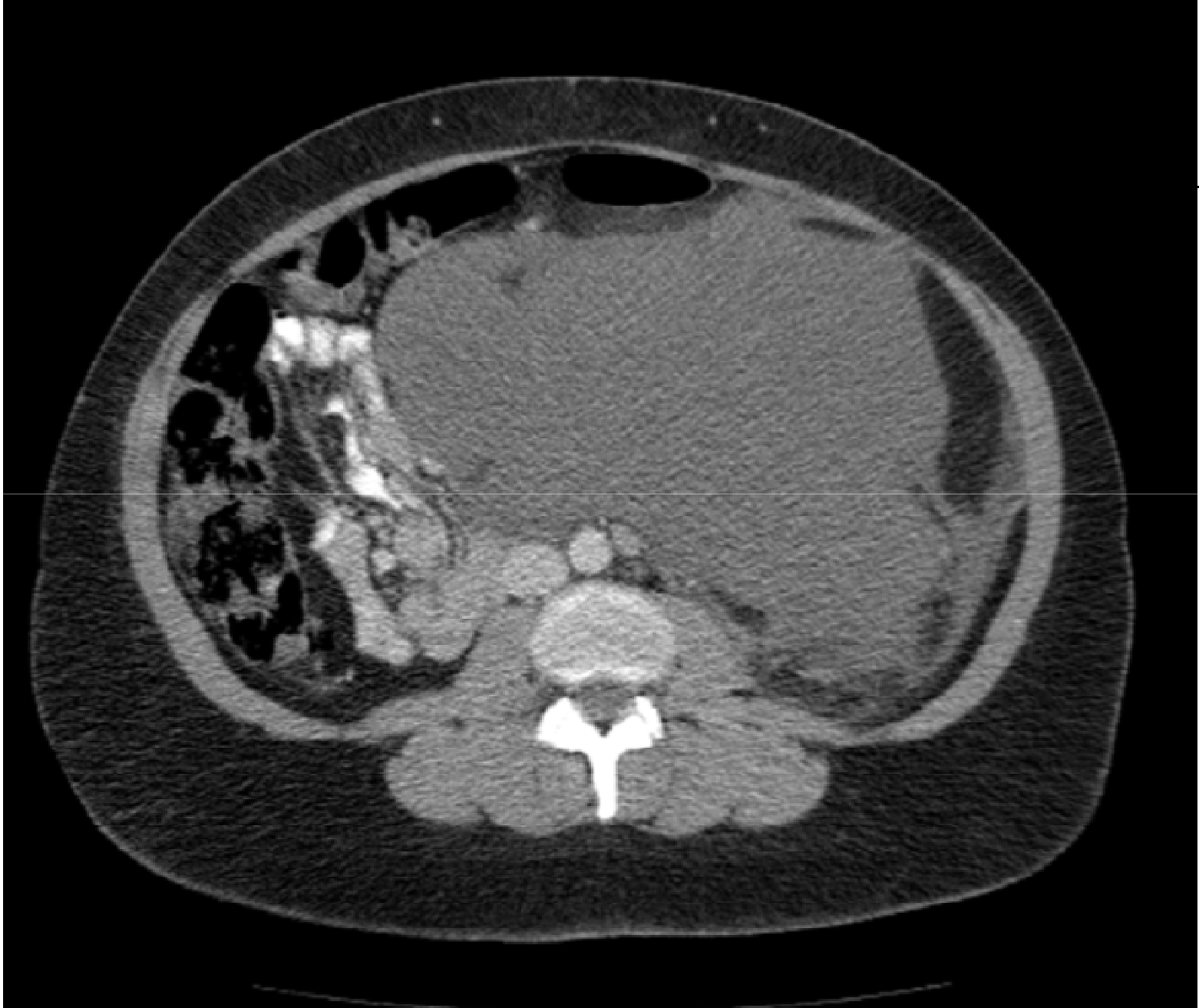


Potential strategies to improve local control

Question – is a positive margin over a critical structure with resection of adjacent uninvolved organs around the rest of the tumour, better than a simply marginal resection with complete macroscopic clearance all around the tumour?

Is one positive margin better than two positive margins in relation to overall survival?







Potential strategies to improve local control

Tumour biology

or

Surgical ability





Potential strategies to improve local control

Two European studies (2009)

- Advocating a policy of more liberal visceral en bloc resections to include an envelope of normal tissue/uninvolved adjacent organs around the tumour to improved local control

Bonvalot S, et al Primary retroperitoneal sarcomas: A multivariate analysis of surgical factors associated with local control. J Clin Oncol 2009;27:31–37.

Gronchi A, et al Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. J Clin Oncol 2009;27:24–30.



French report

- 382 patients - retrospective data from an unspecified number of institutions across France over a 20-year period including primary/recurrent disease
 1. Complete compartmental resections (systematic complete resection of uninvolved contiguous organs)
 2. Simple complete resection/shelling out
 3. Contiguous involved organs resected
 4. Gross residual disease
- Radiotherapy 32%
- Chemotherapy 15%, 31%, 63%: (Grade 1, 2, 3)
- Intra-operative tumour rupture 20%



French report

Local recurrence (multivariate analysis)

- High grade (HR 2.57)
- No tumour rupture (HR 2.33)
- Negative histological margins (HR 1.88)
- High volume centres (1.61)
- Compartmental resections vs simple complete vs contiguous involved (HR 1.99, HR 2.17)



French report

No difference in overall survival
(multivariate analysis)



Italian report

- 288 patients, primary RPS(193) or first recurrence (95)
- Compared the patient group where liberal visceral en bloc resections were performed (after 2002) to a group prior to this approach (before 2002)
 - Systematic excision en bloc with surrounding tissue even when not infiltrate
- No overall survival benefit achieved



Italian report

- The local recurrence rate was lower in the group where more aggressive surgery was performed
 - 5 yr LR rate early 48% vs late 28%
 - follow-up early 120 months vs late 32 months
- Multivariate analysis recurrence-free survival
 - Liposarcoma (HR 2.91)
 - Grade II/III (HR 1.7/HR 2.51)
 - Early group vs late group (HR 0.64)



Italian report

- No overall survival benefit was achieved.



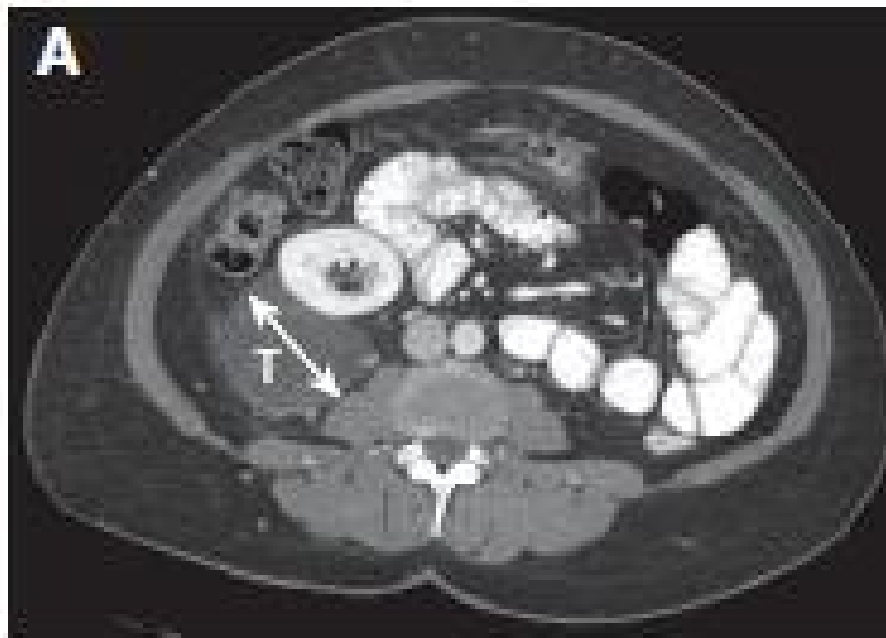
Potential strategies to improve local control

Pisters editorial raises shortcomings of these studies

- Unavoidable selection biases in retrospective studies
- Liberal approach of resecting uninvolved adjacent organs was used selectively (? tumour biology)
- Neither of the studies standardized operative techniques, reporting of imaging or pathology specimens.
- Further confounded by the use of pre- or postoperative radiotherapy in 31 and 32% of patients respectively

Pisters PW: **Resection of some—but not all—clinically uninvolved adjacent viscera as part of surgery for retroperitoneal soft tissue sarcomas.** J Clin Oncol 2009;27:6–8.

Selection bias





Potential strategies to improve local control

- “We need to thoughtfully consider these data, the limitations resulting from selection bias, the safety issues surrounding this before recommending it as standard treatment outside the context of high-volume centres.”
- “Hypothesis generating...thought provoking... suitable to the occasional patient with a small favourably located RPS”
- “We should not change our clinical practice until prospective evidence is provide”



Conclusion

- The ability to completely resect a retroperitoneal sarcoma and tumour grade remain the most important predictors of local recurrence and disease-specific survival.
- There is, as yet, no evidence to support the argument that extended surgical radicality over and above gaining complete macroscopic clearance impacts on survival.



Conclusion

- Complete macroscopic excision should be the goal of surgical resection and are associated with lower incidence of local recurrence and improved survival.
- Further trials and research is required to determine the role of combined-modality therapies to improve local control and disease-specific survival.

The ROYAL MARSDEN

NHS Foundation Trust



Thank you