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Neoadjuvant therapy in limb  
threatening sarcomas – Should we  
really leave it to the surgeons?

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LIFE

Neoadjuvant therapy in ~~limb~~  
threatening sarcomas –  
Should we really leave it to  
the surgeons?

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- Neoadjuvant
  - The delivery of a treatment modality prior to the definitive surgery
  
  - Neoadjuvant modalities
    - Radiotherapy
    - Chemotherapy
    - Isolated limb perfusion
    - Chemoradiation

# Neoadjuvant treatment – What are the aims?

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- Downstaging the tumour to improve operative outcomes
  - Limb salvage
  - Enable R<sub>0</sub>
  - Improved post-operative limb function
- Minimise risk of local recurrence
- ?Improve survival

# Surgery alone

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- Surgery is the mainstay in localised soft tissue sarcoma
- Historical outcomes from surgery alone
- Stout et al (1906 – 1946)
  - 259 patients                      LRR:        61%
- Cantin et al (1968) 1935-1959
  - 653 patients trunk and extremities
  - LRR    29%
- Gerner et al (1975) 155 patients with extremity or trunk STS
  - amputation                      LRR 8%
  - Wide local excision            LRR 60%
  - “Local” excision                LRR 93%
- 1970s: Enneking introduced radical compartmental resections
- Improved local control
- Fewer amputations
- Still high number of local recurrences ~15-20%

# Surgery Alone.....

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- Principal “curative” treatment modality
- However,
- Local recurrence rate 10-20%
- 5 year overall survival rate 60%
- Can neoadjuvant therapies improve these figures?

# Improving local control

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**Radiotherapy accepted modality in improving local control in high risk tumours**

- **Stout et al 1975**
  - 100 patients “simple excisions” post op radiotherapy
  - LRR 13% (historically expect >30%)
  
- **Rosenberg 1982**
  - Randomised to amputation vs LSS and radiotherapy (16:27)
  - No difference in overall survival or DFS
  - No LR in amputation 4/27 LSS
  - Only correlate for LR – positive margins

# Advantages of preoperative radiotherapy

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- Requires smaller field sizes
  - Plan to include only clinically and radiologically involved tissue
  - Post operative: also include drainsites and other surgically involved areas
- Requires lower doses
- Relationship between higher doses and poorer functional outcome

# Preoperative radiotherapy – it is not a new question?

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6. Scott, W. G.: Chairman's Address: The future potential and evaluation of preoperative radiation. Proc. Fifth National Cancer Conference, Philadelphia, J. B. Lippincott Co., 1964; pp. 458-459.

# Preoperative radiotherapy

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- Used sporadically from mid 1930s to mid 1970s
- Suit et al (1985)
  - Non randomised review of 100 patients treated with either post operative or preoperative radiotherapy
  - No differences in LRR/OS

# Randomised Preoperative vs postoperative radiotherapy with LSS

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- O'Sullivan et al (2002)
  - Extremity STS any grade (83% HG) or size (33% >10cm)
  - Randomised Preop (93) vs post op (94)
  - Preoperative dose 50Gy/25# (post op boost if R1)
  - Postoperative (65Gy/32#)

# O'Sullivan et al

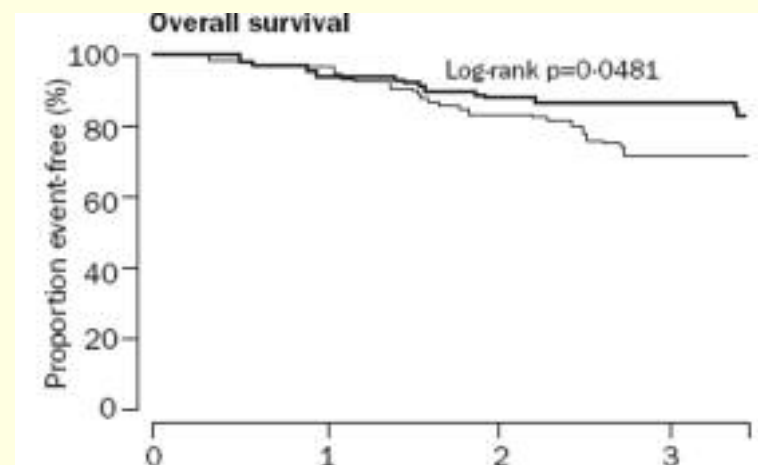
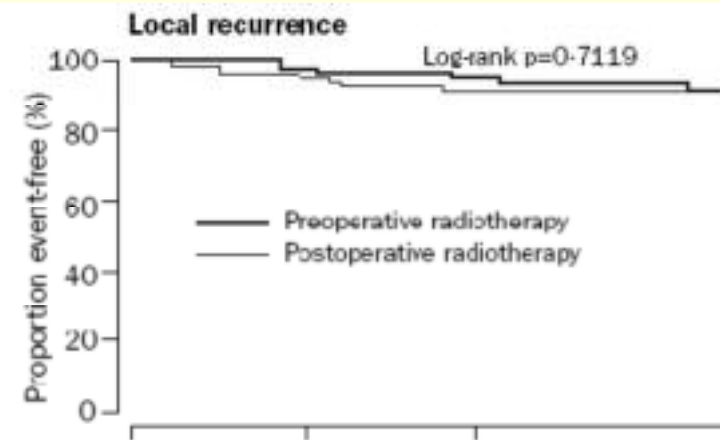
- Outcomes:
- Wound complications:

	Preoperative (n=88)	Postoperative (n=94)
<b>Wound complications*</b>		
Yes	31 (35%)	16 (17%)
Secondary operation for wound repair	14 (45%)	5 (31%)
Invasive procedure for wound management†	5 (16%)	4 (25%)
Deep wound packing deep to dermis in area of wound at least 2 cm with or without prolonged dressings >6 weeks from wound breakdown‡	11 (35%)	7 (44%)
Readmission for wound care§	1 (3%)	0
No complications	57 (65%)	78 (83%)

- $\geq$ Grade 2 acute skin toxicity significantly greater in postop group ( $P>0.0001$ )

# O'Sullivan et al

- Equivalency in LRR
- Trend toward improved OS in preop
- Worse function at 6 weeks for preop
- Equivalent function at 2 yrs
- Need longer f/u re long term morbidity and effect of preop vs postop
- Higher wound complications balanced by potentially lower long term morbidity



# What about neoadjuvant chemotherapy?

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## ■ Potential roles:

- Downstaging local disease -?change surgery
- Improved local control rate
- Upfront treatment of micrometastatic disease
- Determination of chemosensitivity

## Disadvantages

- Delays time to definitive surgery – risk of progression to inoperability
- Chemotherapy toxicity delaying time to surgery

# Neoadjuvant chemotherapy

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- Active agents in soft tissue sarcomas

RR (>50% )

- Single agent doxorubicin: 20-25%
- Doxorubicin + ifosfamide: 30-35%

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RR (>50% )

- Single agent doxorubicin: 20-25%
- Doxorubicin + ifosfamide: 30-35%
- Would reductions of >50% change the type of surgery

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RR (>50% )

- Single agent doxorubicin: 20-25%
- Doxorubicin + ifosfamide: 30-35%
- This means that this degree of reduction only happens in 1/5 to 1/3 patients
- In at least 1/3 of patients “best” response is PD
- Potential to compromise operability in already at risk limb

# Little supportive data:

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- Most small retrospective reviews
- MD Anderson (Pisters) 76pts (1986-90)
  - Stage IIIb extremity STS (med size 10cm)
  - All preop chemo: most dox based (only 3 ifos)
- Responses: CR+PR 28%  
SD 43% PD30%
- No difference in rate of local recurrence
- No difference in survival

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Either no change in surgery  
or risk of worsened surgical  
outcome

# EORTC Phase II randomized study comparing NAC to surgery alone

- High risk extremity STS
- Chemotherapy Dox 50mg/m<sup>2</sup>+Ifos 5G/m<sup>2</sup> x3 cycles
- 67 randomized to each arm

High Risk	
Size	Grade
≥8cm	Any
<8cm	II/III
Local Recurrence	Any
R1 within 6wks	II/III



# Phase II randomized study comparing NAC to surgery alone

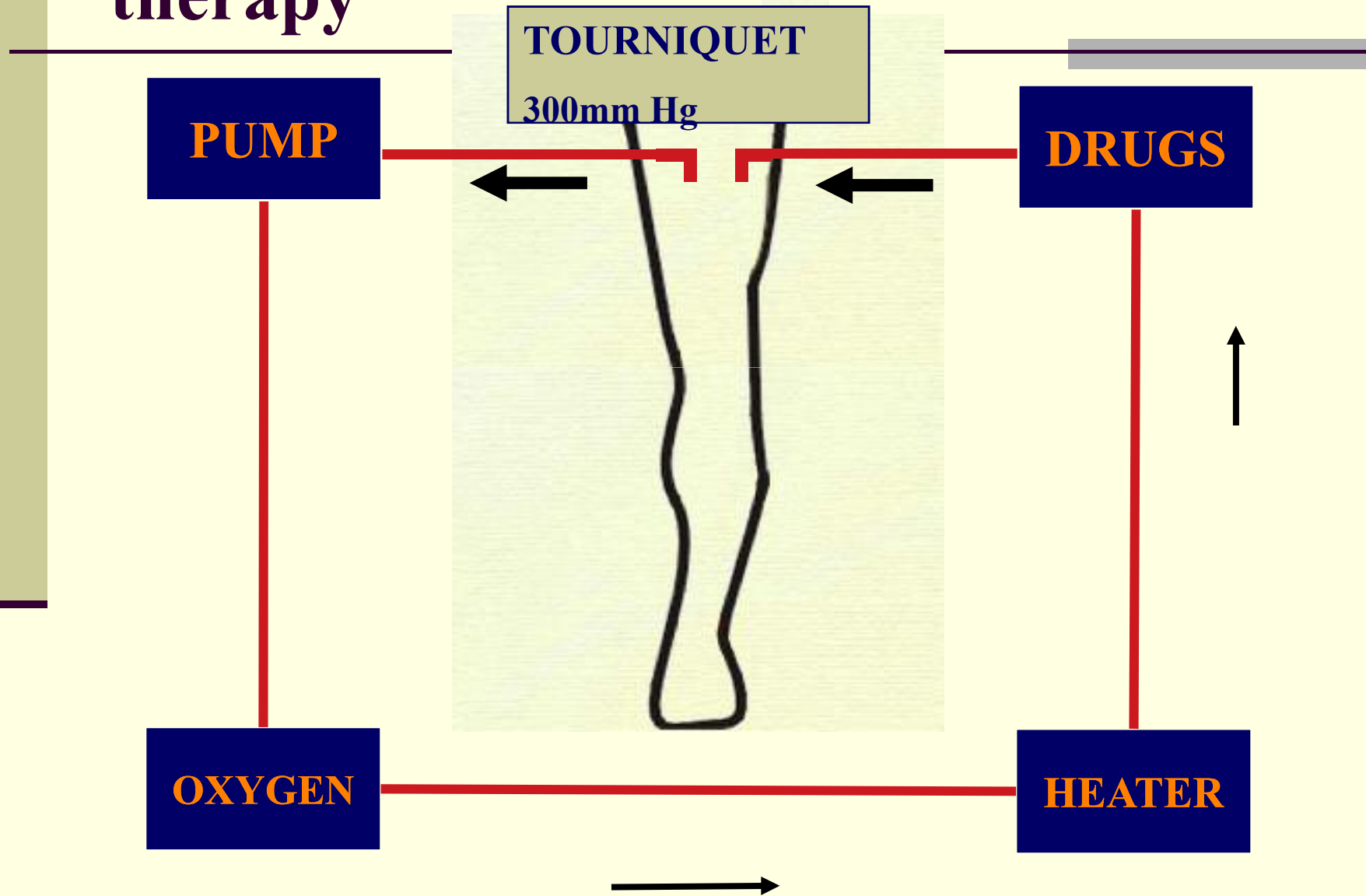
- Surgery – LSS 88%
  - Amputation 12%

(all as per plan at time of randomisation)

	No preoperative chemotherapy	Preoperative adjuvant chemotherapy
Planned/performed surgery		
Amputation	6/6	9/9
Compartmental resection	22/24	13/17
Wide excision	27/24	32/28
Marginal excision	7/11	9/10
No information	3/0	1/0
Total	65/65	64/64
Microscopical radicality		
Radical	57 (88%)	58 (91%)
Irradical	8 (12%)	6 (9%)

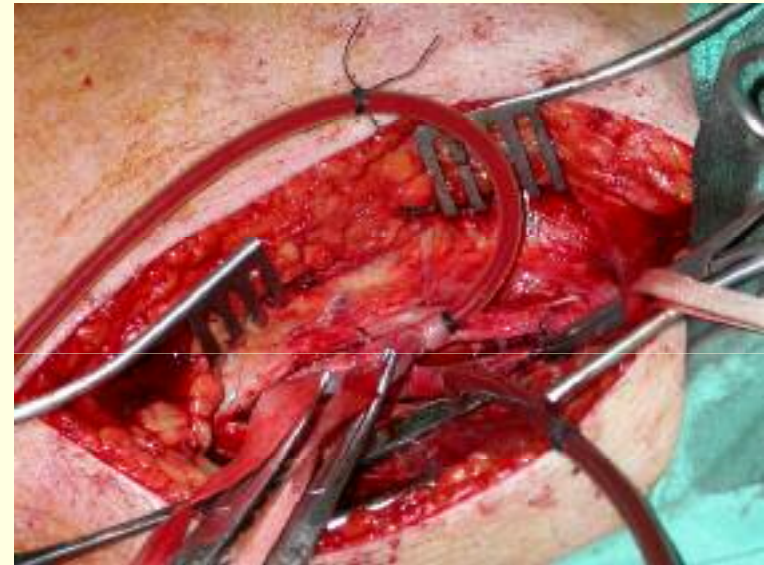
NAC did not “downstage” the planned surgical technique, nor improve R1-R0

# Isolated limb perfusion as a neoadjuvant therapy



# Isolated limb perfusion

- Technique for regional delivery of chemotherapy at doses 10 fold of systemic tolerance
- Limb isolated and supply vessels cannulated
- Perfused with melphalan +TNF 1 hour then wash out
- Mild hyperthermia 38.5-40°C



# ILP – role of melphalan in STS

- Chemotherapy agents: melphalan\*\*\*
- Others trialled include cisplatin and doxorubicin
- Melphalan alone not highly effective in sarcoma

<b>Sarcoma</b>	<b>CR (%)</b>	<b>PR (%)</b>	<b>Author</b>
n=17	0	35	Krementz 1977
n=51	6	12	Muchmore1983
n=17	0	18	Pommier1988
n=13	7	0	Klaase 1989

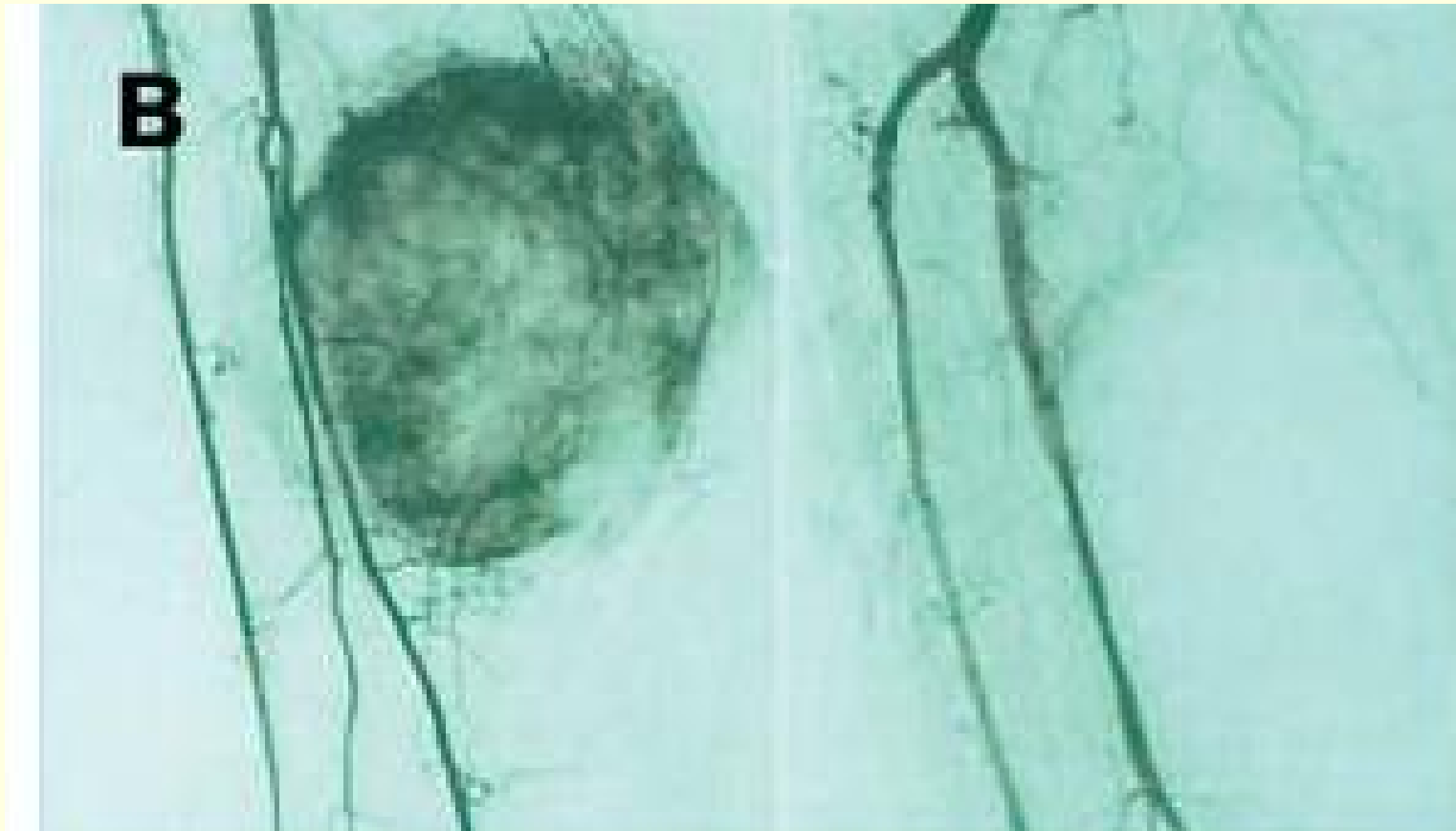
# Tumour Necrosis Factor - TNF $\alpha$

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- Direct vascular effects
- Early effect
  - Increased endothelial permeability (targeting of endothelial cadherin)
  - Increased penetration of melphalan (x4) to tumour
  - Appears to be to some extent tumour vasculature specific
- Late effects
  - Disruption of cell-cell adhesive junctions
  - Inhibition of integrin signalling
  - Endothelial cell death
  - Destruction of tumour associated vasculature

# Angiograms before and after TNF ILP

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*Eggermont et al Lancet Oncol July 2003*

# Response rates for sarcoma to ILP with melphalan and TNF- $\alpha$

<b>Sarcoma</b>	<b>CR (%)</b>	<b>PR (%)</b>	<b>Author</b>
<b>n=186</b>	<b>18 (29*)</b>	<b>57 (53*)</b>	<b>Eggermont1996</b>
<b>n=246</b>	<b>17 (27*)</b>	<b>48(48*)</b>	<b>Eggermont 1999</b>
<b>n=35</b>	<b>37*</b>	<b>54*</b>	<b>Gutman1997</b>
<b>n=20</b>	<b>26*</b>	<b>64*</b>	<b>Rossi 1989</b>
<b>n=217</b>	<b>16*</b>	<b>68*</b>	<b>Gruenhagen 2006</b>
<b>n=100</b>	<b>35</b>	<b>22</b>	<b>Bonvalot 2005</b>

# Two distinct roles for ILP in the treatment of extremity sarcoma

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- Salvage treatment for irresectable sarcoma with no option for post perfusion surgery other than amputation
- Induction chemotherapy for large sarcomas that are resectable by standard surgical approaches - NEOADJUVANT

# Only surgical option is amputation...

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- Late onset primary lymphoedema
- Presented early 2007 with rapidly progressive angiosarcoma in lower leg and thigh
- Only amputation feasible hindquarter but lymphoedema above amputation limit
- Failed systemic chemotherapy



September 2007



December 2008

# TNF- $\alpha$ melphalan Isolated Limb Perfusion at the RMH

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*Annals of Surgical Oncology* 14(1):230–238  
DOI: 10.1245/s10434-006-9040-x

## Isolated Limb Perfusion With Melphalan and Tumor Necrosis Factor $\alpha$ for Advanced Melanoma and Soft-Tissue Sarcoma

Andrew J. Hayes, MD, PhD, Susan J. Neuhaus, MD, PhD, Matthew A. Clark, MD, and  
J. Meirion Thomas, MD

Department of Surgery, Sarcoma and Melanoma Unit, The Royal Marsden Hospital, Fulham Road, London SW3 6JJ,  
United Kingdom

# ILP at the RMH: (Hayes et al)

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- 49 consecutive ILP's (30 melanoma 16 sarcoma 3 other) 2000-2004
- 39 femoral, 5 axillary, 3 popliteal, 2 iliac
- Median follow up 14 months
  
- Sarcomas were inoperable – this was not used as neoadjuvant therapy

# Outcome

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A. J. HAYES ET AL.

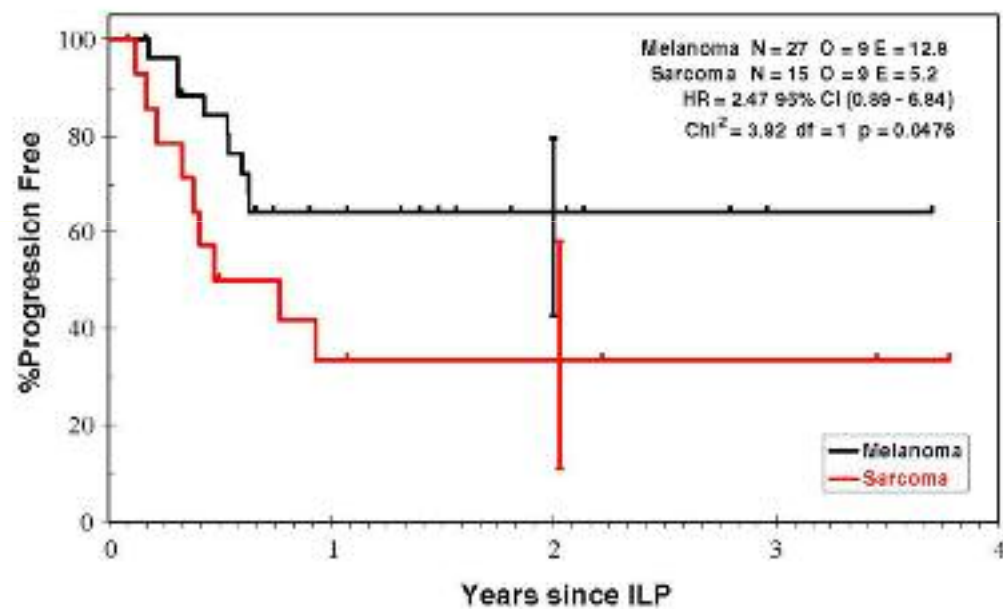
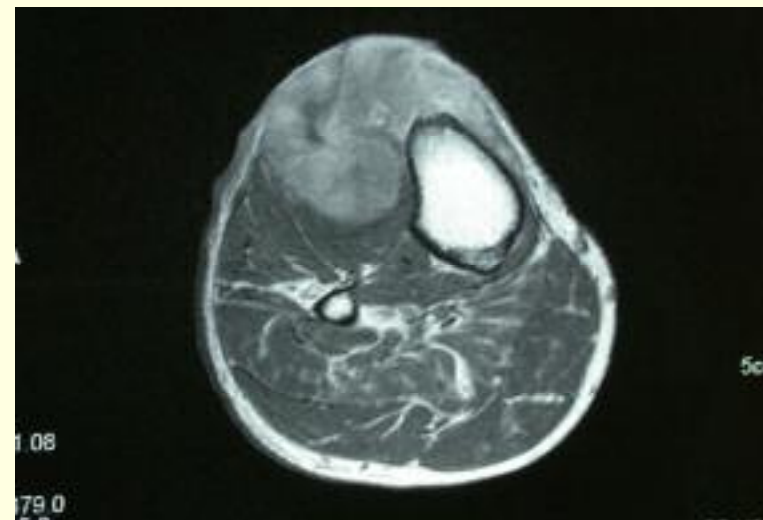
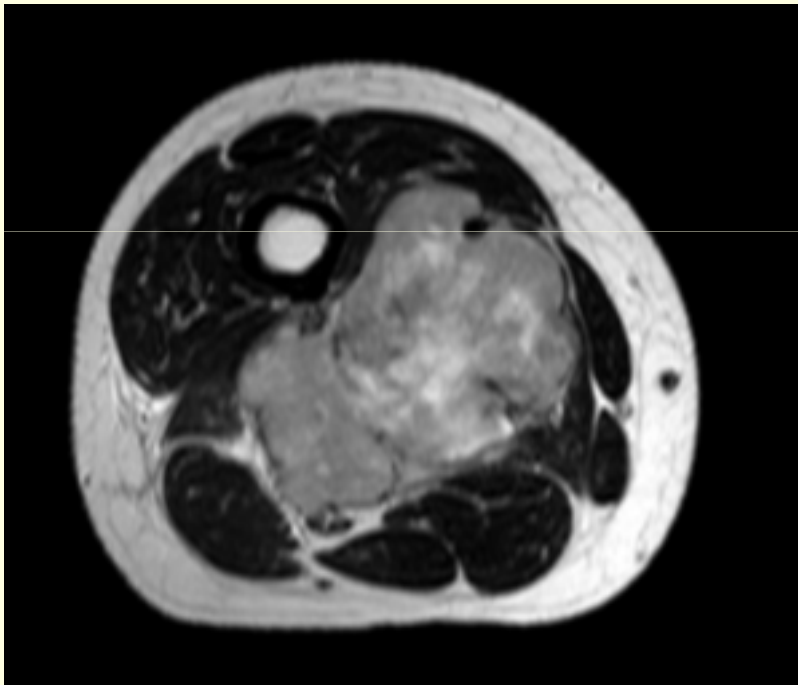


FIG. 3. Kaplan-Meier curves of progression-free survival (local disease) for patients with sarcoma and melanoma. There was a statistically significant difference between the two curves ( $P = .0476$ ; hazard ratio [HR], 2.47; 95% confidence interval [CI], .89–6.84). ILP, isolated limb perfusion; O, observed; E, expected.

# Outcome

<b><i>Response</i></b>	<b><i>Melanoma# (n=27)</i></b>	<b><i>Sarcoma/ (n=15)*</i></b>
<b>Complete response</b>	<b>11 (40%)</b>	<b>3 (20%)</b>
<b>Partial response number</b>	<b>10 (37%)</b>	<b>5 (33%)</b>
<b>% patients who subsequently progressed locally (after initial response)</b>	<b>10 (37%)</b>	<b>10 (66%)</b>
<b>Median time to progression In months (range)</b>	<b>Median 6 (1-8)</b>	<b>Median 5 (1-17)</b>
<b>% patients requiring subsequent amputation</b>	<b>0</b>	<b>4 (27%)</b>

Neoadjuvant: “Unresectable”  
disease treated by ILP then surgery  
for the tumour remnant



# Eggermont et al: 1996

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- 186 patients – “Irresectable”
- Large (16cm )-high grade-62% in thigh
- Planned marginal resections 2-4 months post ILP
- Results
  - CR 29% PR 53% PD 2%
  - 82% limb salvage
  - 126 pts with single tumours resected – LRR 11%
  - 60 not operated on: 55% local control (45% LR)
  - Additional radiotherapy in only 11%
  - Authors note more additional post-treatment radiotherapy may have improved outcomes

# Bonvalot et al: 2005

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- Randomised study of ILP with varying doses TNF with melphalan in unresectable STS
- 100 patients
- Aim delayed en-bloc resection 2-3 mos post ILP
- Results
  - Dose no effect on response
  - OR (CR+PR) 52-72%
  - 84% surgery (13=amputation)
  - $R_0 = 35$   $R_1 = 32$
  - Adjuvant radiotherapy in 37 patients
  - 2year LRR 27%
  - Correlation between recurrence and margin

# Role of ILP as neoadjuvant...

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- Very active treatment strategy for tumour response
- Are these tumours truly irresectable?
- Does it improve LRR in those with positive margins compared with adjuvant radiotherapy.
- Could radical surgery with reconstruction if necessary and post operative radiotherapy have achieved similar low LRR
- RMH: large thigh tumours: radical surgery followed by adjuvant radiotherapy
  - Local recurrence rate: 15%
  - Amputation rate 5%

# In conclusion....

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- Surgery is the mainstay of localised STS
- Neoadjuvant therapy aims to
  - Improve surgery
  - Improve local control
  - Improve survival outcomes

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- Neoadjuvant radiotherapy –
  - Defined role for radiotherapy in localised STS
    - Preoperative allows for lower dose and smaller field
    - Less radiation toxicity and probably improved function compared with adjuvant radiotherapy
    - Increased wound complications
  - Useful in planned R1 resection where smaller field or lower dose important

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- Neoadjuvant chemotherapy
  - Little evidence for improved survival
  - May improve local recurrence rates
  - Very selected cases only – very chemosensitive (eg myxoid LPS/synovial sarcoma)
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- Neoadjuvant ILP
  - Some evidence to demonstrate ability to improve operability
  - No evidence that any better than radical surgery and radical dose radiotherapy

# Thank you

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