

Soft Tissue Sarcoma: Standard Therapies

How Physicians Choose What to Recommend

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I will be discussing off-label use of agents to treat sarcoma

A Brief Introduction

There are over 50 different subtypes of sarcoma, together comprising 1% of cancer in adults

Oncologists in general practice may only encounter a given subtype once or twice in their careers

Guidelines exist to assist in treatment selection (NCCN)

- Detailed, assembled by experts, frequently updated
- Can be difficult to have all the context necessary to choose “optimal” therapy
- www.nccn.org
 - The Patient Resources Section is excellent

Systemic Versus Local Therapies

- Local Treatments: Radiation and Surgery
 - Treat only a specific part of the body
- Systemic Treatments: Putting medicine in the blood stream to treat entire body
 - Attacks any lesions that might be seen on scans in metastatic patients
 - Attacks other microscopic disease that you DON'T see
- Adjuvant Treatment: Treating patients at high risk for tumor recurrence after surgery

Classes of Systemic Therapy for Soft Tissue Sarcoma


Traditional Cytotoxic Chemotherapy

- Attacks the machinery used by cells to duplicate their DNA, grow, and divide
- Side Effects: Hair loss, bone marrow suppression, infertility

Targeted Agents

- Inhibits specific genes or proteins that the cancer uses to grow or feed itself
- Side Effects: High blood pressure, wound healing complications, skin changes

Immunotherapy

- Checkpoint Blockade: take the “breaks” off the immune system so it can see and fight the cancer
 - Side Effects: Autoimmune disorders including hormone problems
 - Still mostly experimental in sarcoma
- 

Approved/Commonly Used Agents for Soft Tissue Sarcoma

Cytotoxic Chemotherapy:

- Doxorubicin, Ifosfamide, Dacarbazine, Gemcitabine, Docetaxel, Eribulin, Trabectedin

Targeted Agents:

- Pazopanib, Regorafenib, Everolimus, Temsirolimus

Immunotherapy:

- Pembrolizumab, Nivolumab, Ipilimumab

Other special cases: Imatinib, sunitinib, and others...



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NCCN Recommended First Line Therapy: Metastatic Disease

Preferred Regimens:

- Doxorubicin
- Doxorubicin and Dacarbazine
- Doxorubicin and Ifosfamide (AIM)
- Liposomal doxorubicin
- Epirubicin (and combinations)

Other Recommended Regimens:

- Gemcitabine
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Doxorubicin

- A derivative of a compound isolated from soil bacteria
- Works by interfering with the replication of DNA
- Possible Side effects include:
 - Nausea
 - Mouth sores
 - Weakening of the heart muscle
 - Decreased blood counts
 - Second cancers
- Used at lower doses to treat breast cancers, leukemias, lymphomas, and others

Doxorubicin in Sarcoma: Dose Matters!

No. 5

ADRIAMYCIN DOSE RESPONSE • O'Bryan *et al.*

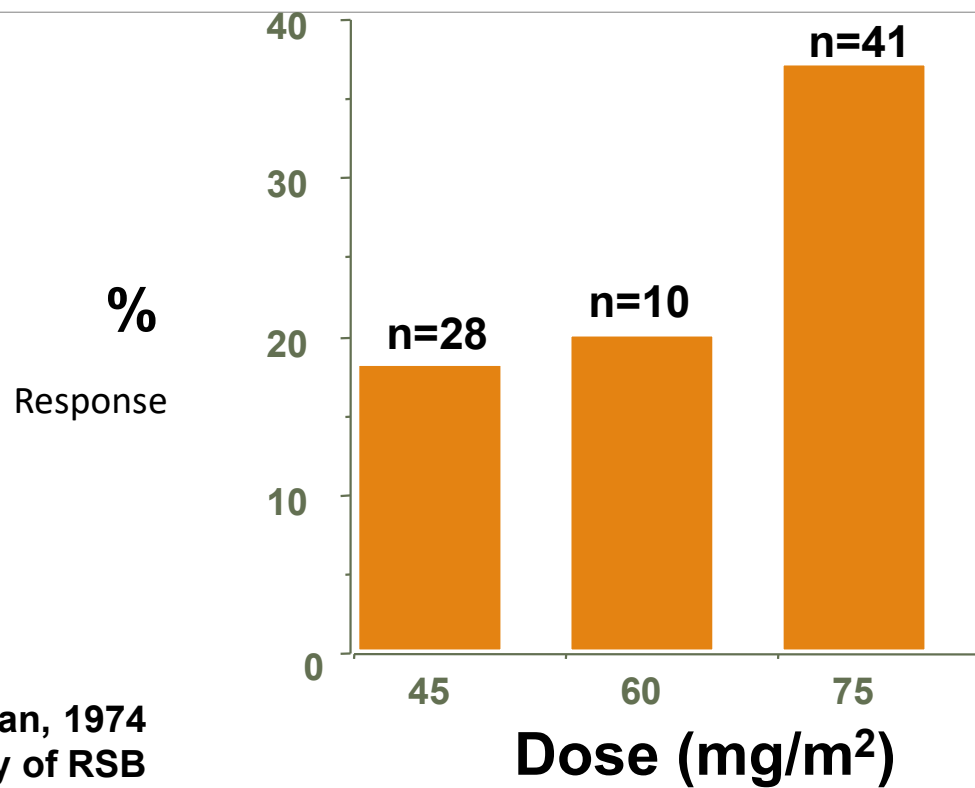
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TABLE 3. Remissions According to Dose Schedule and Tumor Type
(#) Remissions/(#) Patients (% Remissions)

Tumor type	Good risk			Poor risk	
	75 mg/m ²	60 mg/m ²	45 mg/m ²	50 mg/m ²	25 mg/m ²
Lymphoma	9/23 (39)	4/7 (57)	6/17 (35)	7/25 (28)	7/22 (32)
Hodgkins	4/11 (36)	2/3 (66)	1/4 (25)	2/9 (22)	2/8 (25)
Thyroid	6/14 (43)	0/3 (0)	3/5 (60)	0/4 (0)	0/3 (0)
Sarcoma	15/41 (37)	2/10 (20)	5/28 (18)	1/9 (11)	0/10 (0)
Breast	11/44 (25)	10/27 (37)	11/32 (32)	8/34 (24)	2/34 (6)
Bladder	6/17 (35)	2/7 (29)	3/20 (15)	0/11 (0)	0/10 (0)
Prostate	3/10 (30)	2/4 (50)	0/5 (0)	0/7 (0)	0/12 (0)
Lung	1/19 (5)	2/6 (33)	3/18 (17)	0/6 (0)	1/7 (14)
Head & Neck	0/8 (0)	0/2 (0)	2/12 (17)	2/10 (20)	0/6 (0)
Ovary	3/24 (13)	0/9 (0)	1/12 (8)	0/8 (0)	1/5 (20)
Kidney	1/14 (7)	0/8 (0)	0/6 (0)	0/5 (0)	1/5 (20)
Other	7/38 (18)	2/9 (22)	2/32 (6)	1/3 (33)	3/16 (19)
TOTAL	66/263 (25.0)	26/95 (27.4)	37/191 (19.4)	21/131 (16.0)	17/138 (12.3)

O'Bryan, RM. *et al. Cancer.* 1977

Doxorubicin Dose-Response in Sarcomas



O'Bryan, 1974
Slide Courtesy of RSB

Doxorubicin: Protecting the Heart

Doxorubicin is often given as a 15 minute infusion

- Most non-sarcoma patients receive low lifetime doses

Increasing the infusion time (48-72 hours) decreases cardiac damage

- Increases the incidence of mouth sores

Dexrazoxane is a medication that can be given to protect the heart from doxorubicin

- Expensive but usually covered by insurance
- Cancer outcomes seem to be similar, but limited data on this
- Variable practices on when it is used

Doxorubicin Based Combinations: Dacarbazine

Study	A Dose	AD Dose	Response Rate (A vs AD)	CR rate (A vs AD)	Survival (A vs AD)
Gottlieb et al 1977	N/A	A - 60 mg/m ² D - 1000 mg/m ²	41%*	5%	Not Reported
Omura et al 1983	A - 60 mg/m ²	A - 60 mg/m ² D - 1000 mg/m ²	16 % vs 24 %	6.3% vs 10.6%	7.7 vs 7.3 mos
Borden et al 1987	A - 70 mg/m ²	A - 60 mg/m ² D - 1000 mg/m ²	18 % vs 30 %	5.3% vs 6.5%	8.0 vs 8.0 mos

- Combination described in the late 70s due to non-overlapping toxicity
- Improved response rate
- No demonstration of overall survival benefit (but that is hard to show)

* Response based on clinical criteria

A Response on Doxorubicin and Dacarbazine



Ifosfamide

- Available since the 1970s, but caused bleeding in the bladder
- Mesna is a compound that prevents bladder hemorrhage
- Possible Side effects:
 - Kidney injury
 - Neurotoxicity
 - Other overlapping side effects
- Also used to treat lymphomas, testicular cancer, and other tumors
- Has a Dose-Response relationship similar to doxorubicin

Doxorubicin and Ifosfamide (AIM)


- Made possible by the availability of white cell growth factors (filgrastim, PEG-filgrastim)
- Nearly double the response rate over doxorubicin alone in a recent study
 - Overall survival trends better, but not definitive
- This has been the de-facto 1st choice front line combination regimen for fit patients who require tumor shrinkage

Concerns with combination therapy

- Combination treatments result in higher response rates
- Comes at the price of more side effects, hospitalizations, etc
- Controversy over whether giving drugs together extends life

What Are The Goals of Therapy?

Doxorubicin With or Without Ifosfamide

- Combination therapy is definitely better when tumor shrinkage is required
 - There is variability in practice in asymptomatic patients with metastatic disease
 - Both doxorubicin alone and in combination, correct dosing is important
 - Ask about cardioprotection, practices around this are variable
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- A solid orange horizontal bar spanning the width of the slide, located at the bottom.

Adjuvant Systemic Treatment

- Adjuvant Therapy: Chemotherapy given to patients who are “cancer free” in order to decrease chance of recurrence
- If this is done before surgery, its called “neoadjuvant” therapy
- Key Considerations:
 - Identify patients at high risk of recurrence
 - Identify a treatment that lowers that risk
 - Don't treat patients who are unlikely to benefit

Adjuvant Systemic Treatment

Table 7. Five-Year Actuarial Rate of DM in Patients Who Achieved Local Control of Soft Tissue Sarcoma Versus Size of Sarcoma

Tumor Size (mm)	Grade 1		Grade 2 and 3	
	No. of Patients	DM (%)	No. of Patients	DM (%)
≤25	5	0	17	6
26-49	11	0	48	23
50-100	12	0	55	38
101-150	4	0	24	49
151-200	4	0	9	58
>200	2	0	6	83
Total	38	0	159	35

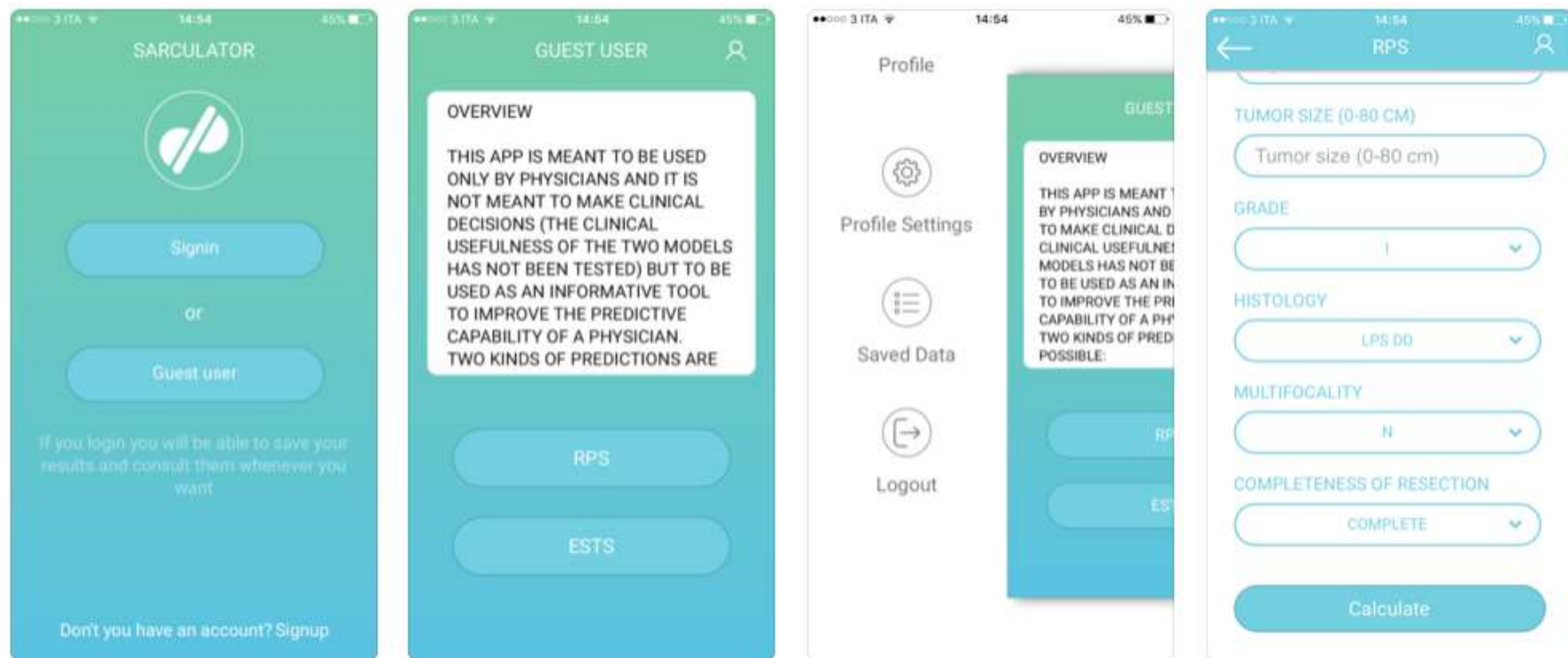
Key Risk Factors for Metastatic Disease

- FNLCC Grade
- Size of Tumor
- Specific Sarcoma Type

Suit, H. *et al. J. Clin. Onc.* 1988

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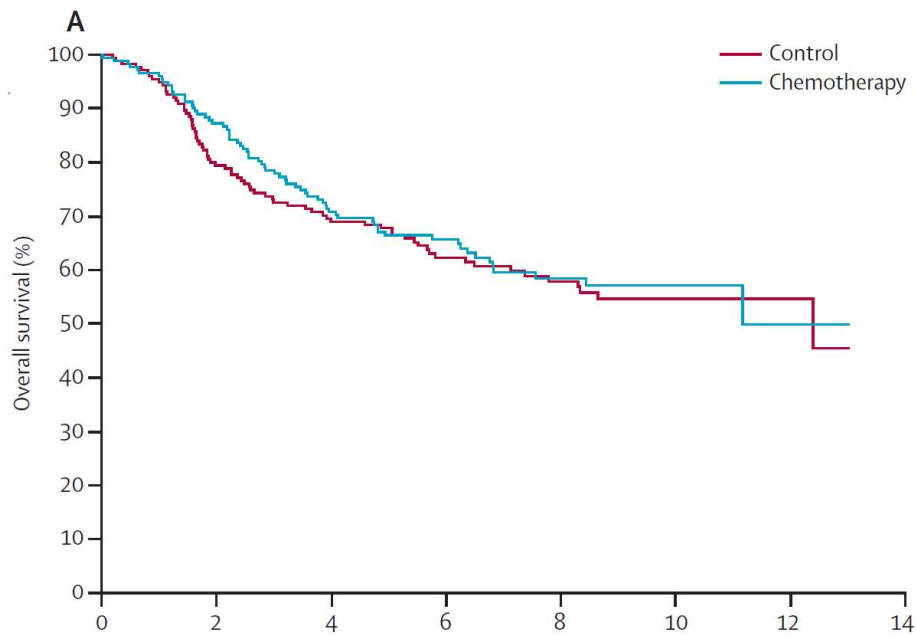
Risk Stratification: The Sarculator



Adjuvant Treatment: Reasons for Controversy

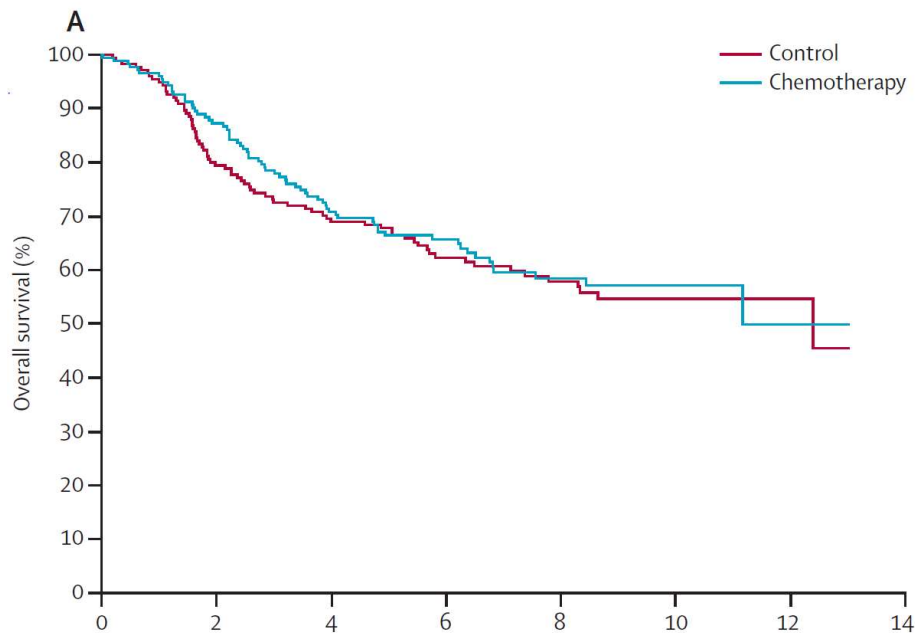
- Whether adjuvant chemotherapy works has been a controversial topic
- Trials of adjuvant therapy are limited by:
 - Heterogeneous patient populations
 - Older studies using outdated regimens
 - Discomfort randomizing high-risk patients to no treatment
 - Historically, few trials demonstrating clear benefit

EORTC 62931



- A high quality study using a modern chemotherapy regimen versus no chemotherapy
- No difference in overall survival

EORTC 62931:



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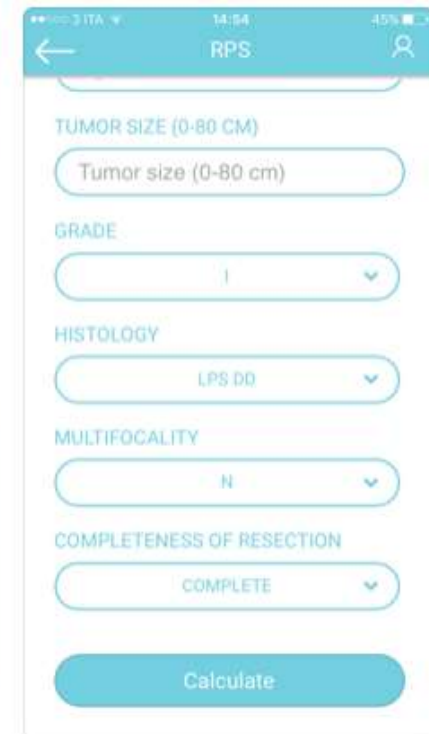
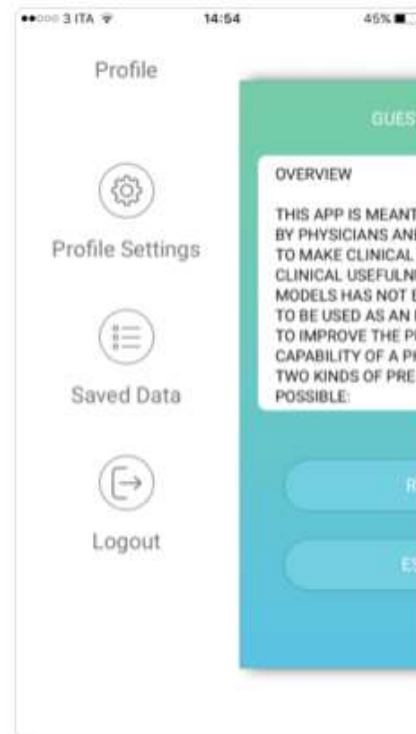
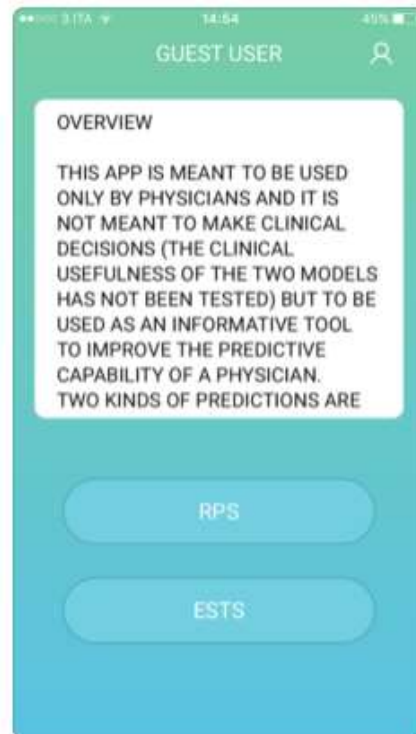
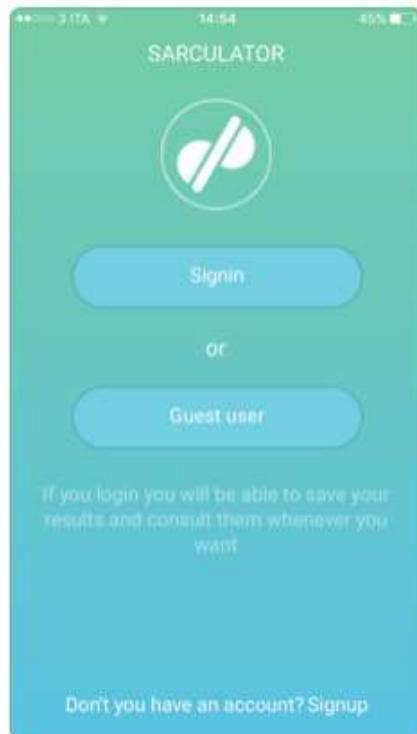
- Key critique is that many patients were not high risk

- 40% of tumors were grade II

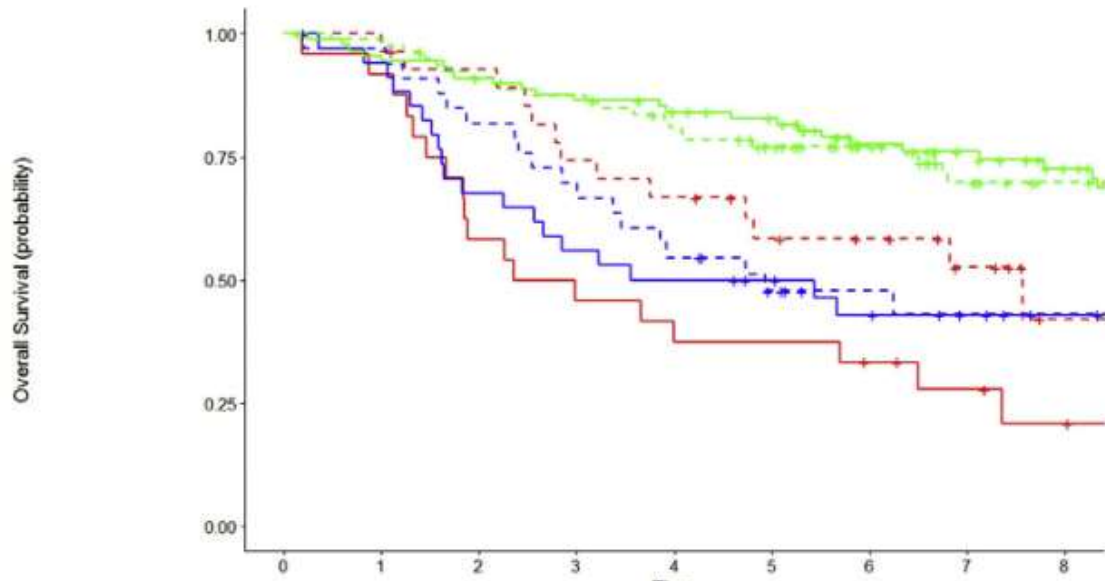
- Tumor size from 0.3-35 cm (median 8.6 cm)

Woll 2012

Risk Stratification and EORTC 62931



Adjuvant Chemotherapy: EORTC 62931 Revisited

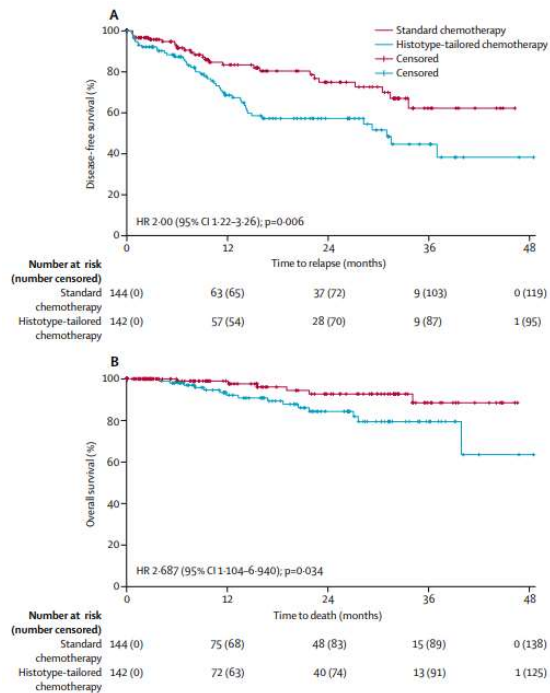


Using the Sarculator nomogram, 60% of enrolled patients were low risk (predicted overall survival at 10 years greater than 66%)

Examining only those with pr-OS of less than 51%, adjuvant chemotherapy **halved** the risk of death

Pasquali 2019

ISG-STS 1001: Histotype Specific Therapy



In a **high risk** patient population with sarcomas that are **sensitive to chemotherapy**, neoadjuvant epirubicin and ifosfamide showed an improvement in overall survival over other sensible therapies

Adjuvant Therapy: Summary

- Adjuvant/neoadjuvant chemotherapy for soft tissue sarcomas has been a controversial topic
- Differing opinions on who “qualifies”
- Doxorubicin and ifosfamide is the treatment of choice for adjuvant therapy

Parting Thoughts

- Consultation with a sarcoma specialist is vital in ensuring optimal treatment selection
 - Agent selection
 - Dosing and cardioprotection
 - Appropriateness of adjuvant systemic therapy
- Many sarcomas regimens are straightforward to administer in the community— others require close monitoring
- Second opinions can be helpful, and you don't need to be shy about it

Thank You!

