INTRAOPERATIVE RADIATION THERAPY FOR RETROPERITONEAL SARCOMA

ISIORT 2014

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NOTHING TO DISCLOSE

SOFT TISSUE SARCOMAS

2014 Estimated cases in the USA

12,020 diagnosed (0.7% of all cancers)

4,740 deaths (0.8% of all cancers)

Retroperitoneal sarcomas

15% soft tissue sarcomas ~1800 cases/year (0.11% of all ca's)

IN CONTRAST TO EXTREMITIES:

Majority of deaths are due to uncontrolled abdominopelvic disease

A rare tumor……where local control is important

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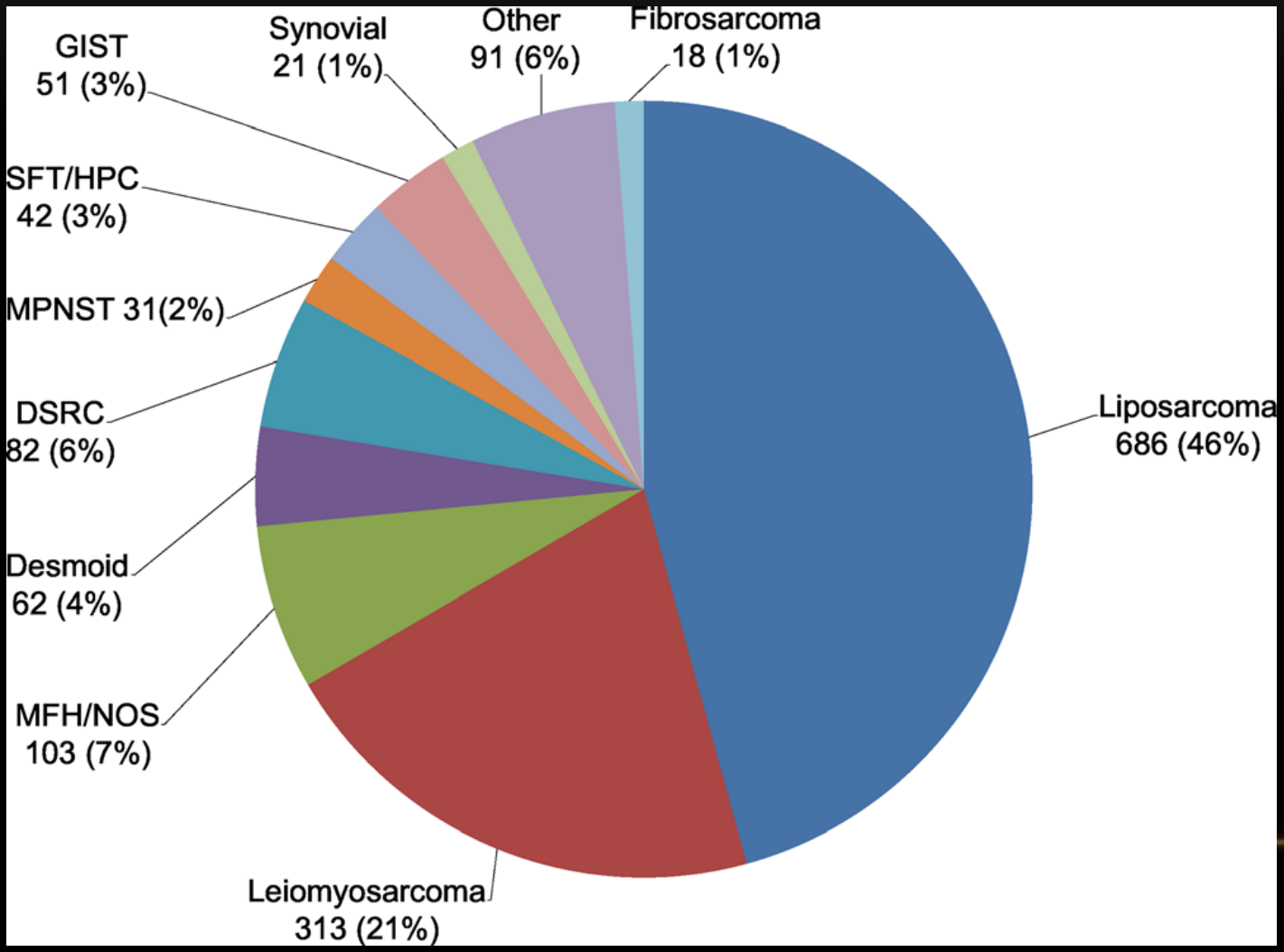

Histologic subtypes of RP sarcomas 1500 case from MSKCC/ 30 years

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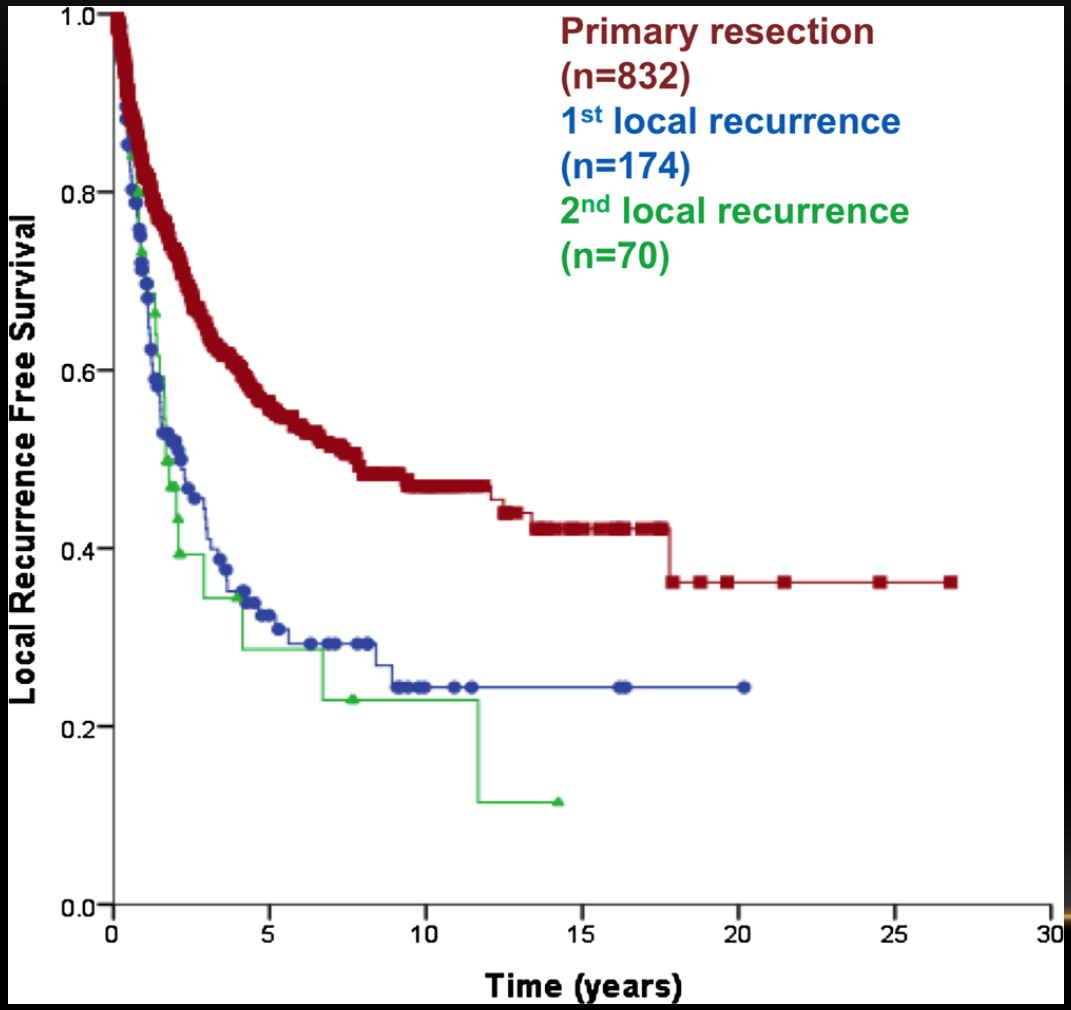

Local recurrence free survival
- >1,000 patients at MSKCC

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Complete surgical resection - standard of care for RP sarcomas

- Most reports segregate R0-R1 vs R2
- Extent of appropriate surgery/margins debated:
  - Tumor/'simple" excision
  - Continguously involved organs
  - Complete compartment –removal of 'uninvolved continugous organs
- Most common organs removed: kidney, colon, psoas

  Also: pancreas, adrenal, diaphragm, small bowel, IVC, bladder
- Some discussion that type of resection needs to be tailored to the biology of the disease (grade/histopahtology)

Bonvalat S JCO Jan2009; Strauss DC Br J Surg Mar 2010; Mussi C Ann Surg Oncol May 2011

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Surgery -Standard of care for RP sarcomas

Milan: 77 primary disease patients – ~30% preop RT ; 35% pre/postop CT

151 organs resected, extensive path evaluation

some infiltrative – some expansive/pushing types

60% (92/151) of organs had involvement of tumor

80% patients had at least one viscera involvement

type of involvement varied with histology: LMS/non-lipoid sarcoma-infiltrative; expansive-liposarcoma

No difference of OS/Local disease free survival with more extensive surgery

5 year OS 73%/LDFS 52% (median FUP 17.5 months)

Mussi C Ann Surg Oncol May 2011

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French: 382 patients

65 simple, 130 contiguous organ, 120 compartment resections

38 gross residual, 21 re-excisions

80 preop chemotherapy; 110 postop radiation

Compartment resection – 3.29-fold lower rate of abdominal recurrence

5 year OS 57%/LDFS 52%

Bonvalat S JCO Jan2009

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Royal Marsden: 200 primary patients

- 170 R0-R1 resections
- 126(63%) adjacent organ resections
- 60(30%) with >1 organ removed

Compartment resection – 3.29-fold lower rate of abdominal recurrence

5 year LRFS 55%

- 75% for patients R0-R1 resection

Median time to recurrence 3.8 years

- 6.8 years for patients R0-R1 resection

Strauss DC Br J Surg Mar 2010.

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Summary

Study	N	Median FUP	5 year LC	5 yr OS
Gronchi (collaborative)	523	45 months	66%	57%
UK	200 (all primary)	29 months	55% (75% - R0-1)	na
French (collaborative)	382	53 months	51%	57%
French/Italian (collaborative	249 (all primary)	37 months	78% (crude)	65%

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Why is this important?

- Despite extensive surgery – substantial local failures
- Infiltrative nature/pseudocapsule of sarcomas is not dissimilar to those in the extremity
- Supports the use of preoperative radiation (+/- chemotherapy)

  Postoperative doses exceed normal tissue tolerances of several organs

  To treat the microscopic extent of disease beyond what is planned on resection

  Newer techniques as well as IORT can be used to dose escalate in areas of highest risk

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Hence – question of EBRT is being asked…..

EORTC 62092-22092 STRASS clinical trial

Surgery Alone *vs* Pre-op RT (50.4 GY0 → S

- **Opened Jan 2012**
- **Accrual to date ~ 110 / 256**
- **Primary endpoint: abdominal RFS**

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Techniques used to dose esalate in RPS

- IORT – electrons, HDR brachytherapy
- Postop brachytherapy
- IMRT dose painting
- Protons

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Protons

- Dosimetric study comparing 3DCRT, 3DPRT, and IMRT

  CTV = GTV + 2 cm margin, limited by bone/fascial planes

  All techniques covered CTV

Small bowel dose	V15	V45
3D CRT	66.1%	15.6%
IMRT	52.2%	4.7%
3D CPT	16.4%	6.3%

- Phase I/II MGH study – dose escalation to the posterior abdominal cavity, using both protons and photons

Swanson EL et al IJROBP 2012.

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PMH: Dose escalation with post-operattive brachytherapy:

- 46 pts eligibile for evaluation: 45-50 Gy 3DCRT
- Resection in 95% of pts
- 23 pts received postoperative brachytherapy 20-25 Gy

  Placement dependent on intraop assessment

2 yr OS 88%	97% primary/74% recurrent
	95% low grade/83% high grade
Median FUP	106 months
5–year OS	70%
5-year local control	80.4%
Toxicity	acute:duodenal perfor'n, SBO; late:4 diarrhea/duodenitis-stricture

Smith MJF et al Radiother & Oncol 2014.

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IMRT + IORT

Leuven: 18 patient pilot

- 50 Gy/25 – only high risk area
- 3DCRT and IMRT plans

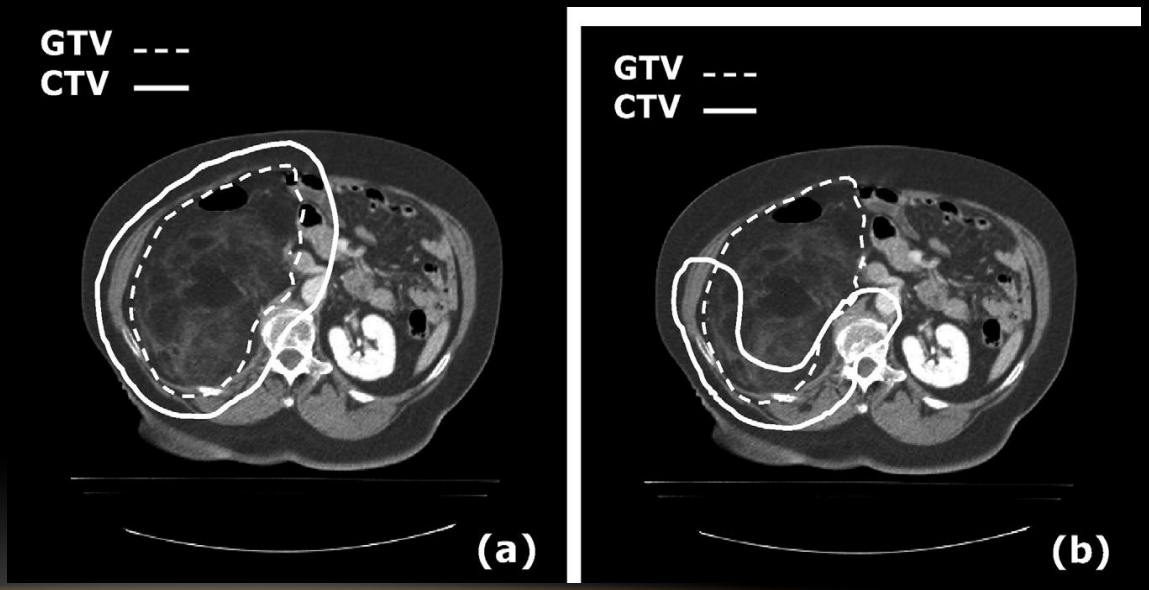
Dose reduced to ipsil kidney

no other DVH improvements

Acute toxicity -2 gr 3 anorexia;

1 gr 2 anorexia, 2 gr 2 nauseas

Bossi A, et al IJROBP 2007.



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U Alabama: 16 pts IMRT with Simultaneous integrated boost

- 45 Gy/25 with SIB 57.5 Gy (surgeon defined volume)

Acute toxicity:only 1 patient with gr 3 nausea

(all other were gr 1 only); no postop problems

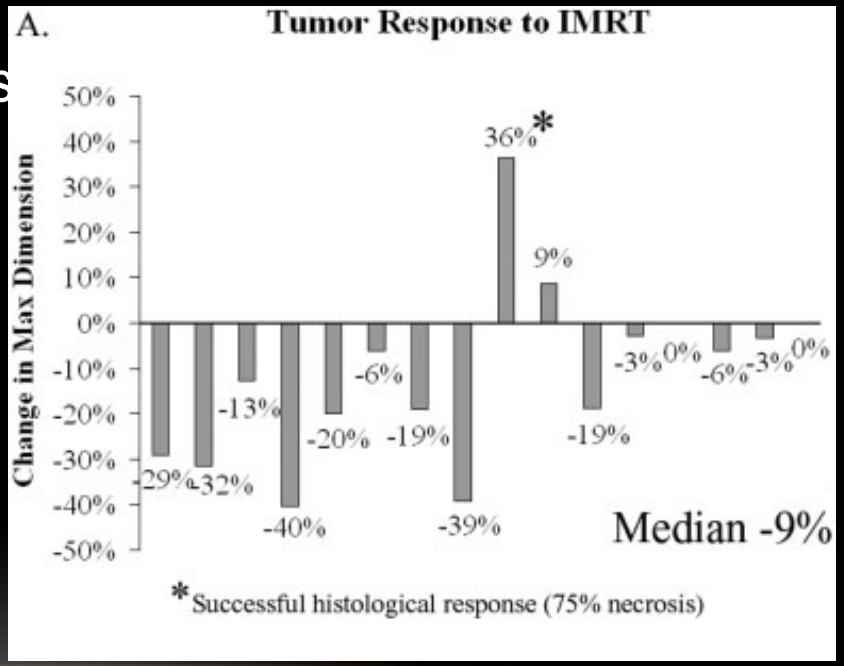
Late toxicity: no severe toxicity, one gr 2

small bowel toxicty

12 tumors (75%) decreased in size/ 2 grew

R0-1 in 14 patients – 1 pCR; 2 LR

Tzeng C-WD, et al Cancer 2006.



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NCI randomized trial : GTR +/- IORT followed by EBRT

- 15 pts: IOERT of 20 Gy +postoperative 35 to 40 Gy EBRT
- 20 pts: postop 50 to 55 Gy EBRT alone (35 to 40 Gy extended field; 15 Gy boost)

Median fup 8 years (minimum 5 years)

	Local recurrence	Median survival	Severe bowel toxicity	Peripheral neuropathy
IOERT/EBRT	3/15 (20%)	45 months	2/15(13%)	9/15 (60%
EBRT	16/20 (80%)	52 months	10/20(50%)	1/20(5%)
P	< 0.001	ns	<0.05	< 0.01

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- Large number of individual institution reports

Study	N (prim/rec)	Median EBRT (pre/post)	IORT	Surgery (R0-R1)	Chemo
Bordeaux 1996	19(38/13)	50 Gy (13 /12)	15-20 Gy	14	9
MSKCC 2000	32(12/20)	45-50 Gy (0/25)	12-15 Gy (HDR)	30	4
MGH 2001	37(29/8)	45 Gy (37/0)	10-20 Gy (13 no IORT)	29	1
France (2003)	24(5/19)	45-50 Gy(7/15)	8-22 Gy	22	5
Stanford 2008	39 -out of 50 pts	47(0/37%)	6-16 Gy (250 KV)	85%	32%
MC AZ 2014	63 (40/23)	45 Gy(22/0)	12.5-17.5 Gy (26 no RT)	56	14

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Study	Median FUP	LC 5 yr	DFS 5 yr	OS 5 yr	Toxicity
Bordeaux 1996	17 months	76%(2 yr)	60% (2 yr)	na	4 postop–1 IORT related/ 4 late
MSKCC 2000	33 months	62% (74 vs 54% for prim/rec)	55%	45%	18% GI. 9% fistula, 6% neuropathy
MGH 2001	38 months	59% (84% w GTR/IORT)	38%	50% (74% w GTR/IORT)	4 pts–2 neuropathy, 2-fistula,
France 2003	52.6 months	50%	28%	56%	6 neuropathy (severe above 15 Gy), ureteral stenosis
Stanford 2008	59 months	26%	25%	na	4 gr 3-4, 2 neuropathies
MC AZ 2014	45 months	89% S-RT/ 46% S	na	60%	34% (neurop-16%, GI-8%,GU-8%)

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MGH Protons +/or IMRT + IORT

28 patients – 20 primary/8 recurrent

Preop RT (75%) – 45 Gy PostopRT (25%) – 45-50.4Gy

89% gross resection

12 pts IORT - reserved for close/positive margins

Chemotherapy – 3 patients

Median fup 33 months

3 yr LRFS 2- 90% primary 3 - 30% recurrent

Yoon SS et al Ann Surg Oncol 2010

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Roedler/Heidelberg: Phase I/II Preop IMRT/Surgery/IORT

27 patients – IMRT (50 Gy) + en bloc resection

- High risk population (>80% gr 2-3, median size 15 cm, extensive surgery)
- Early fup (33 months)
- LC – 72%/ 7 yrs – 2 outside EBRT/ 2 late recurrences
- DM - 8 pts

Toxicity – 9 postop complications (2 deaths)

- 15% acute toxicities
- 5% late toxicity

Roedler, ASTRO 2014.

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Outcome comparisons

	N	LC (5 yr)	OS (5 yr)	Toxicity
Heidelberg 2006 – postop	67 (26 primary)	40%	64%	13% ≥ gr2 GI 7.5% ≥ gr2 neuro
Current Heidelberg	27	72%	74%	15% acute 33% postop 5% late

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Acute: Gastrointestinal: nausea/diarrhea

Postoperative

Late: Neuropathy – common, dose dependent, especially over 12.5 Gy

Fistuala

Ureteral stenosis

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Challenges to assessing IORT

1. Merging of both primary and recurrent disease

   -may not the same disease biologically

2. Varying surgical management

   -agreement on resection of involved adjacent organs

   -lack of consensus even among surgical oncologists as to appropriate application of ‘compartment resection’

   - how should the use of radiation (both EBRT and any ‘boost’ therapy- IORT/IMRT/other) be modified based on surgical plans

3. Varying dose/timing of EBRT

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Future directions

- EORTC study – evaluate the role of radiation
  - Is the radiation dose sufficient?
- Evaluate use of external beam dose escalation
  - Will this substitute for IORT?
- Continue to pool data for similar biologic diseases
  - Further define the unique aspects of different sarcomas
- Improved biologically directed therapy for use in the treatment of BOTH local as well as systemic spread of disease

THANK YOU