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Practical Approach to Desmoid Tumours

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Lloyd Mack
Surgical Oncology
University of Calgary

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Objectives:

- To appreciate the evolving treatment of desmoid tumours – from surgical disease to multidisciplinary condition

- To describe a surgical approach to desmoid tumours based on their biologic aggressiveness

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Classification of Soft Tissue Tumors

- Locally recurring ST neoplasm with little or no metastatic potential
- Sarcomas with metastatic potential of LESSER aggressiveness
- Aggressive Sarcomas

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Locally Recurring Soft Tissue Neoplasms with Little or No Metastatic Potential

- Desmoid Tumour
- Atypical Lipomatous Tumour
  - Low grade liposarcoma
- Dermatofibrosarcoma proturberans
  - (DFSP)

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Definition

- **Synonyms** – musculoaponeurotic fibromatosis, deep fibromatosis, aggressive fibromatosis, desmoid tumor, well-differentiated nonmetastasizing fibrosarcoma, grade I fibrosarcoma
- Locally aggressive, histologically benign neoplasms with unpredictable growth, invasion, and symptoms including pain, deformity, dysfunction, and possible death
- No metastatic potential; do not de-differentiate

Weiss and Goldblum Soft Tissue Tumors 2001
Lewis et al Ann Surg 1999;229:866-73
Schajowicz et al Cancer 1995;75:1208-14

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Presentation

- Incidence 2-4/ million/ yr
- Present as a **mass** in general locations
  - Intra-abdominal/ Mesenteric (5-10%)
  - Abdominal wall (20%)
  - Extra-abdominal – limb, chest, breast, neck (65-70%)
- Young adults, peak incidence 30 years, 2/3:1/3 female:male gender distribution, majority are solitary (5% multicentric), majority are sporadic (95-98%)

Ballo et al J Clin Oncol 1999;17:158-67
Gronchi et al J Clin Oncol 2003;21:1390-7

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Etiology

- Unclear
- Trauma, especially surgical trauma
- Hormonal – 2/3 female, may grow during pregnancy

- Genetic – Familial Adenomatous Polyposis
  - Aka Gardner's syndrome
  - 1/5 patients with FAP will develop desmoid tumours
  - 1000 x greater than population
  - ≈2 years after surgery; median age 30; usually intra-abdominal

Groen et al Ann Surg Oncol 2008;15:2439-50

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Evaluation

- **History**: lump or swelling
  - ?growth plateau, ?regression
  - location specific symptoms
- **Physical Examination**
  - size, superficial vs. deep
  - neurovascular evaluation, deficits
- **Investigations**
  - plain radiographs, U/s to confirm mass
  - CT or MRI to define location, margins, relation, heterogeneity

Guglielmi et al Radiol Med 2009;114:1292-1307

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Biopsy Approach

- Image directed core biopsy
  - Multiple samples sufficient to make diagnosis in 90% of STS
- Incisional biopsy
  - Same principles as STS
- Excisional biopsy
  - Unusual since deep
- Review by expert soft tissue pathologist
  - Well-differentiated intertwining fibroblasts in bundles with abundant collagen matrix

Welker et al Cancer 2000;39:2677-86
Hoeber et al Ann Surg Oncol 2001;8:80-7

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Surgical Principles

- Treatment should be tailored – consider multidisciplinary input up front
- **Ideal** – surgical resection with wide (1-2 cm) gross margin/ pathologically clear margins
- Many **caveats**
  - Surgical resection may not be possible/ feasible
  - Surgical resection may not be possible with negative margins without major disability
  - Role of microscopic margins not clear cut

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Biology…?

When is a Neoplasm not a Neoplasm? When it is a Desmoid

DOUGLAS B. ZIPPEL, MD* AND WALLEY J. TEMPLE, MD
Division of Surgical Oncology, Tom Baker Cancer Centre, Calgary, Alberta, Canada

The Enigma of Desmoid Tumors

Jonathan J. Lewis, MD, PhD,* Patrick J. Boland, MD,* Dennis H. Y. Leung, PhD,† James M. Woodruff, MD,‡ and Murray F. Brennan, MD*

*From the Departments of *Surgery, †Biostatistics, and ‡Pathology, Memorial Sloan-Kettering Cancer Center, New York*

Optimizing Treatment of Desmoid Tumors

Dina Lev, Dhanasekaran Kotilingam, Caimiao Wei, Matthew T. Ballo, Gunar K. Zagars, Peter W.T. Pisters, Alexander A. Lazar, Shreyaskumar R. Patel, Robert S. Benjamin, and Raphael E. Pollock

INDIVIDUALIZING MANAGEMENT OF AGGRESSIVE FIBROMATOSES

MATTHEW A. SPEAR, M.D.,* L. CANDACE JENNINGS, M.D.,† HENRY J. MANKIN, M.D.,† IRA J. SPIRO, M.D., PH.D.,* DEMPSY S. SPRINGFIELD, M.D.,† MARK C. GEBHARDT, M.D.,† ANDREW E. ROSENBERG, M.D.,‡ JAMES T. EFIRD, PH.D.,* AND HERMAN D. SUIT, M.D.*

Departments of *Radiation Oncology, †Orthopaedic Surgery and ‡Pathology, Massachusetts General Hospital, Harvard University Medical School, Boston, MA 02114

Desmoid-Type Fibromatosis: A Front-Line Conservative Approach to Select Patients for Surgical Treatment

Marco Fiore, MD[1], Françoise Rimareix, MD[2], Luigi Mariani, MD[3], Julien Domont, MD[4], Paola Collini, MD[5], Cecile Le Péchoux, MD[6], Paolo G. Casali, MD[7], Axel Le Cesne, MD[4], Alessandro Gronchi, MD[1], and Sylvie Bonvalot, MD, PhD[2]

[1]Department of Surgery, Istituto Nazionale Tumori, Milan, Italy; [2]Department of Surgery, Institut Gustave Roussy, Villejuif, France; [3]Department of Biostatistics, Istituto Nazionale Tumori, Milan, Italy; [4]Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; [5]Department of Pathology, Istituto Nazionale Tumori, Milan, Italy; [6]Department of Radiotherapy, Institut Gustave Roussy, Villejuif, France; [7]Department of Cancer Medicine, Istituto Nazionale Tumori, Milan, Italy

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Biology…?

- Well described variation in growth
  - 50% have period of stability
  - 30% cycles of progression / stability
  - 10% rapidly progress
  - 10% regress/ resolve

- Key study – 198 pts, 68 pts with recurrent desmoid tumours were followed
  - Median f/u 6 yrs; 60 stable, 6 regressed
  - Stability of lesion considered a ‘success’

Church JM Semin Colon Rectal Surg 1995;6:29-32
Rock et al J Bone Joint Surg Am 1984;66:1369-74

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Biology…?

- MD Anderson – comparison of 189 pts from 1965-94 with 189 pts from 1995-2005
- Trends in 2nd compared to 1st time period
  - Increased multimodal therapy
  - Less reliance on surgery alone
  - Higher rates of macroscopic residual disease and equivalent positive margins
  - 5 yr local recurrence 20% vs. 30%
  - More patients had radiation alone (9) or systemic treatment alone (29) – all have remained alive with at least stable disease
  - A subset refused treatment

Lev et al J Clin Oncol 2007;25:1785-91

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Observation?

- **Milan Series –** since 2003, all patients initially recommended a conservative approach (non-operative;no RT)
- 142 pts (74 primary, 68 recurrent)
  - -83 pts had wait and see approach (W&S)
  - -59 pts offered medical therapy (MT)
- 5 year PFS – 49.9% (W&S), 58.9% (MT)
- Multivariate analysis did not identify predictors of stability or regression
- Overall, 1/2 avoided any treatment; 2/3 of pts avoided surgery

Fiore et al Ann Surg Oncol 2009;16:2587-93

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Summary

- **Paradigm shift** – from a ‘cancer’ paradigm to a ‘chronic’ condition
- **Stability** may be a **success**
- **Period of observation warranted**

- **Role of alternate agents and primary irradiation underappreciated**

- **Surgery still has a major role**

Zippel, Temple J Surg Oncol 2007;95:190-1

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Surgical Approach / Principles

- Ideally treatment should be tailored – consider **multidisciplinary** input up front
- **Ideal** – surgical resection with wide (1-2 cm) gross margin/ pathologically clear margins
- Many **caveats**
  - Surgical resection may not be possible/ feasible
  - Surgical resection may not be possible with negative margins without major disability
  - Role of microscopic margins not clear cut
- Need to start somewhere….

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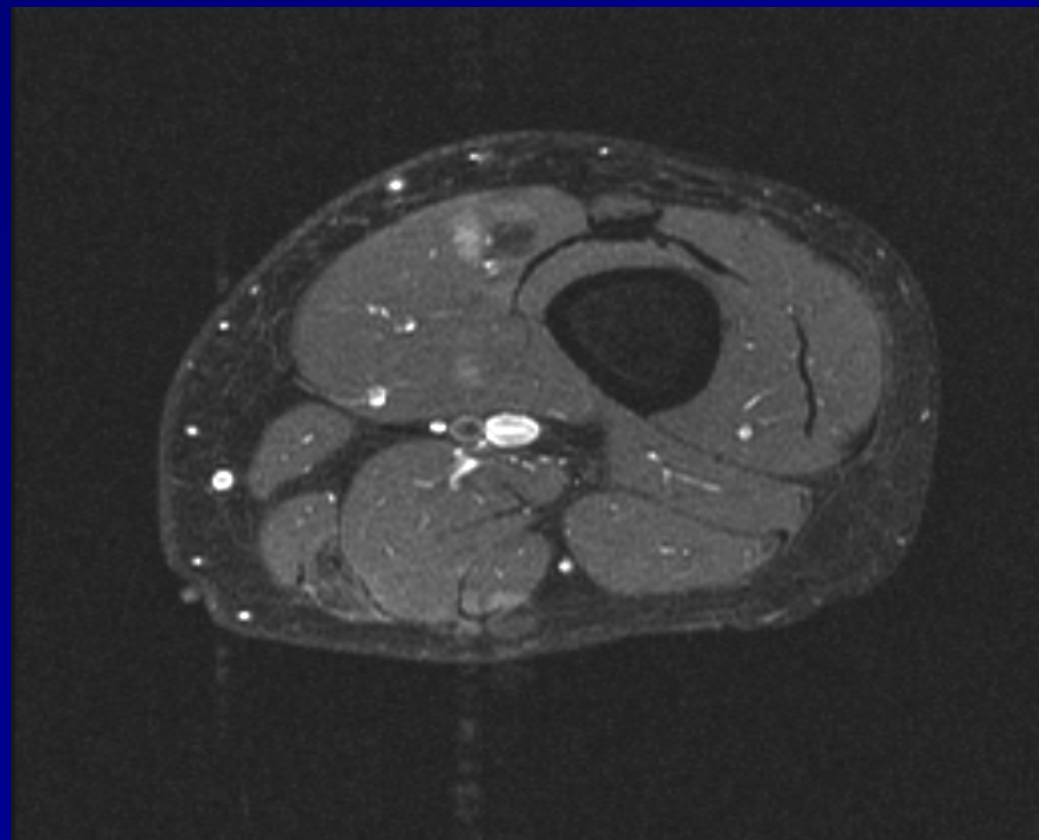
Surgical Approach / Principles

- Consider resection alone when feasible (i.e. easy)

46 y.o. female
4 month hx of painless mass
2.5x1.5cm



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Local Recurrence / Surgery Alone

- Review 22 series, 381 pts – 1983-99
  61% overall local control rate – 72% m-; 42% m+
- Review 12 series, 412 pts – 1969-2003
  45% overall local control rate

Series	Patients (#)	Local Control (5 yr) (%)
MD Anderson	122	66
Milan	198	73
MSKCC	158	77

Nuyttens et al Cancer 2000;88:1517-23 Leithner et al J Surg Oncol 2004;86:152-6
Ballo et al J Clin Oncol 1999;17:158-67 Gronchi et al J Clin Oncol 2003;21:1390-7
Merchant et al Cancer 1999;86:2045-52

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Margins?

- Outcomes influenced by location, proximity to vital organs, and association with FAP
- Significance of positive margins – review of 23 studies
  - Most older studies suggest higher LR with microscopically positive margins; Larger more recent publications have challenged this assumption
  - Local recurrence itself doesn't predict uncontrolled tumor growth
- Options may include re-resection, adjuvant radiation or close follow-up
- If a desmoid has 'stopped' growing, **margin status** becomes **less critical,** especially if function / QoL may compromised

Melis et al J Surg Oncol 2008;98:594-602

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Prognostic Features

- ? Prior recurrence predicts worse outcome
- ? Age (<=30 yrs worse than >30)
- ? Surgery alone worse than combined therapy
- ? Size >5cm >8 cm
- ? Difficult sites – intra-abdominal vs. extra-abdominal or abdominal wall
  - Calf, foot, supraclavicular fossa, popliteal fossa, buttock

Ballo et al J Clin Oncol 1999;17:158-67
Nuyttens et al Cancer 2000;88:1517-23
Catton et al Radiother Oncol 1995;34:17-22

Surgical Approach / Principles

- Consider alternate modalities if not feasible or too disabling

16 y.o. female
2 year hx of slowly growing mass
15x5x3cm; on sciatic nerve

Surgical Approach / Principles

- Consider alternate modalities if not feasible or too disabling

18 y.o. male
U/s screen for polycystic kidneys
Large pelvic mass
11.7x11x9.4cm

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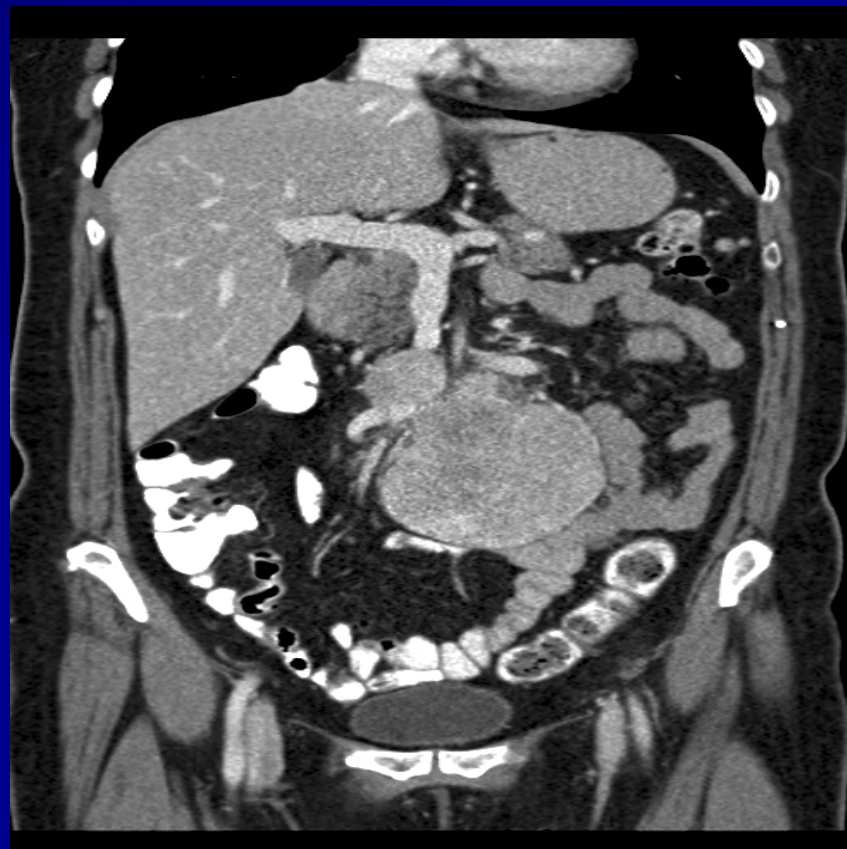
Surgical Approach / Principles

- Consider alternate modalities if not feasible or too disabling

52 y.o. female
Presented with anemia and abdominal mass
Root of mesentery encasing sma/smv



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Alternate Therapy

- Alternate therapies include:
  - Anti-inflammatories, tamoxifen, irradiation as primary treatment, cytotoxic chemotherapy....

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Alternate Therapy

- Tamoxifen/ anti-inflammatories
  - 20-30% overall response rate but stable in 40-50%
  - Sulindac – 10-30% - often in combination
- Cytotoxic chemotherapy
  - 68 patients – median age 32; 2/3 female; 53% had an intra-abdominal tumor; 1/3 had Gardner's; range of surgeries (1-5)
  - 50% had tumors >10 cm; 5 were multifocal
  - Median of 2 lines of chemotherapy (1-7)

  - Best responses with anthracycline agents (35-60%)
  - Vinblastine/ MTX – 30-40%; Imatinib 5-16%
  - Overall – 21% partial response and 15% progressed
  - Progression-free survival – 12 months
  - Median survival – 13 years (FAP); 90% 10-20 year sporadic

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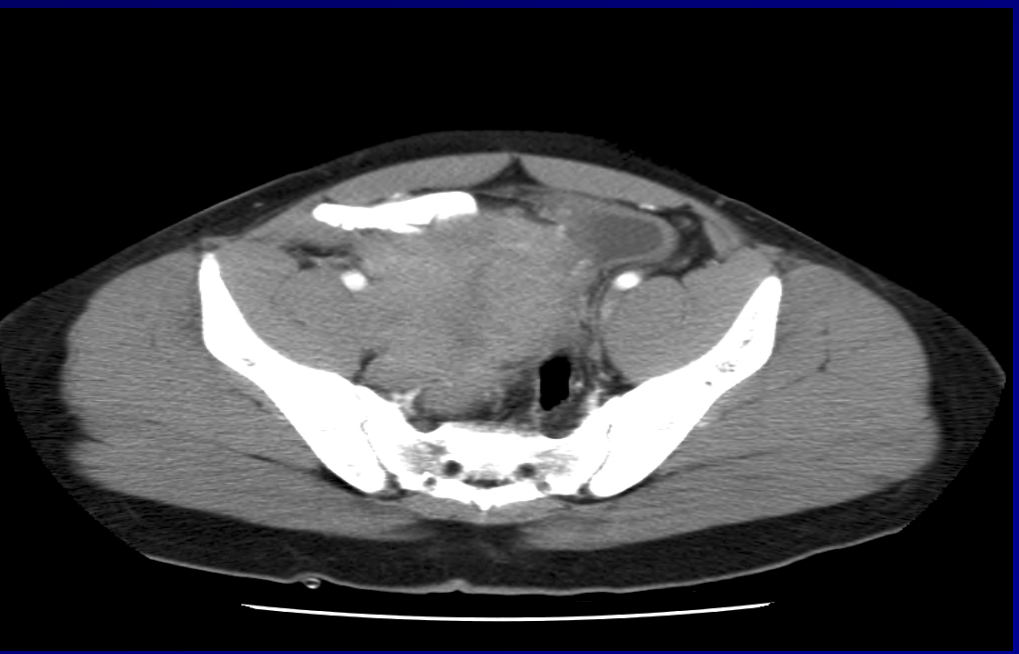
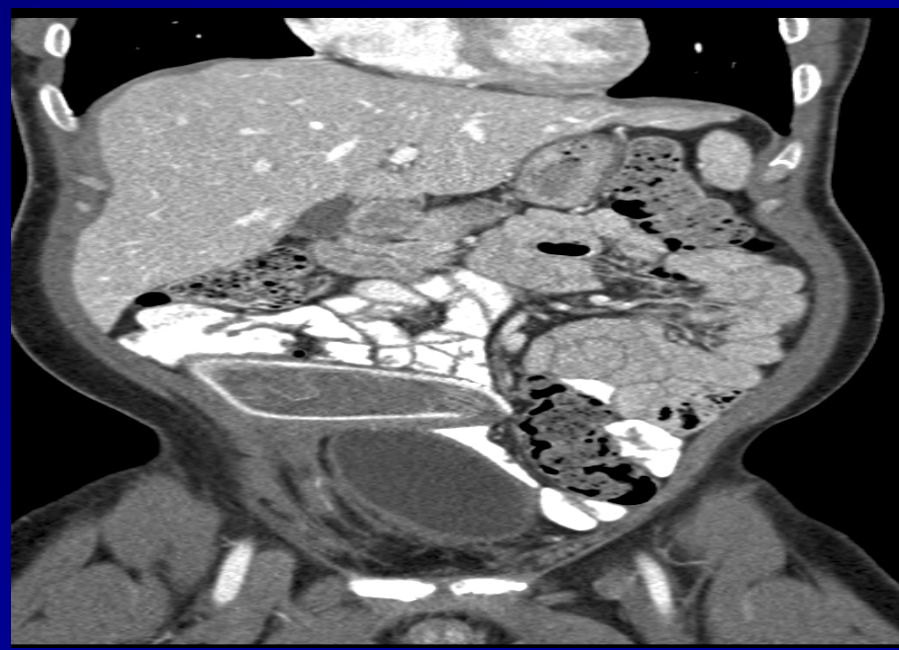
Surgical Adjuncts?

- Surgical Adjuncts?
  - Insertion of spacer to facilitate irradiation
  - Bypass surgery, control of perforation





White et al Ann Surg Oncol 2007;14:583-90

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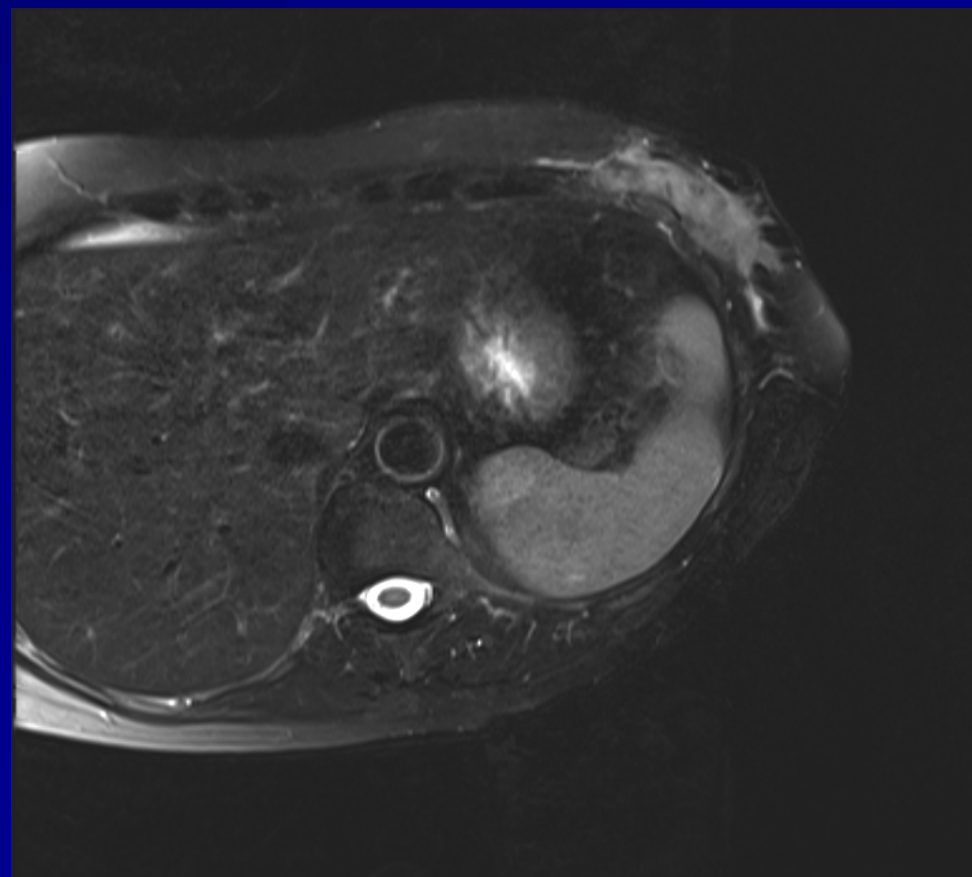
Surgical Approach / Principles

- Is there an operation? Is it possible to get 'good' margins?

60 y.o. female with progressive, painful mass

7x6.8x2.3 cm involving 6-8th ribs



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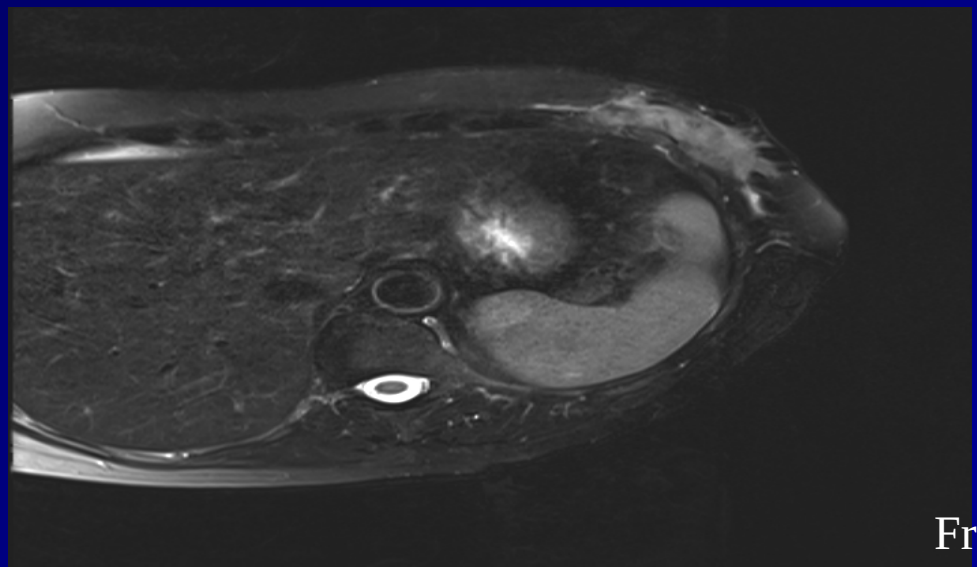
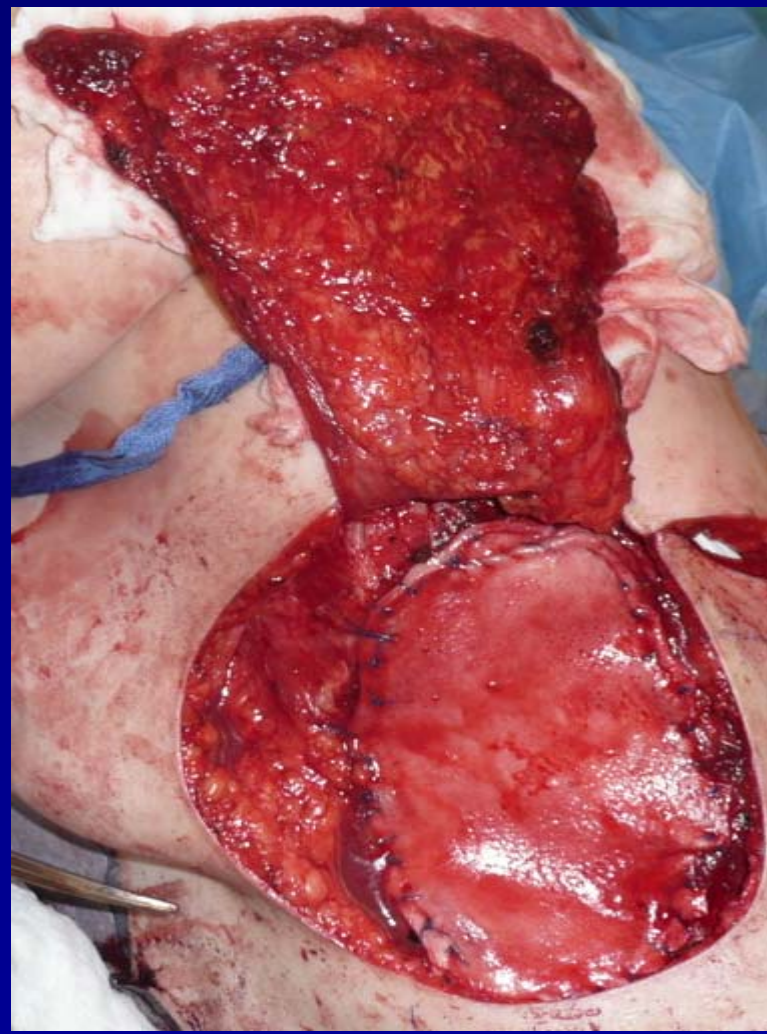
Surgical Approach / Principles

- Is there an operation? YES
- Is it possible to get ‘good’ margins? Difficult
- Patient had preoperative chemoradiation, wide resection including chest wall, reconstruction with alloderm, latissimus flap





Francis et al Ann Surg Oncol 2009:16:1650-4

Surgical Approach / Principles

- Is there an operation? Is it possible to get 'good' margins?

43 y.o. female with initially asymptomatic RLQ mass
7.7x5.1x5.8 cm mass in mesentery
Right hydroureter; intimate with iliac vessels

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Surgical Approach / Principles

- Is there an operation? Yes
- Is it possible to get ‘good’ margins? Unlikely
- Patient had preoperative irradiation (50 Gy) with use of spacer
- Surgery included Rt colectomy, Rt nephrectomy, Iliac vessel resection/ replacement

McKay et al J Surg Oncol 2007;96:151-9

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Surgery as part of Multimodal Treatment

- Review 22 series, 381 pts – 1983-99
- Surgery alone – 61% local control (72m-;41m+)
- Surgery + radiation – 75% (94m-;75m+)
- Primary radiation – 78%

Series	Patients (#)	Local Control (5 yr) (%)
MD Anderson	75	78
UCLA	56	78
U of Florida	72	83

Nuyttens et al Cancer 2000;88:1517-23 Ballo et al Int J Rad Oncol Biol Phys 1998
Goy et al Int J Rad Oncol Biol Phys 1997 Zlotecki et al Int J Rad Oncol Biol Phys 2003

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Surgery as part of Multimodal Treatment

- Comments – differing definitions of local control for primary surgery and primary irradiation; in general patients receiving adjuvant radiation were worse

- Preoperative Radiation

  -less commonly used – 7 pt series

Ballo et al J Clin Oncol 1999;17:158-167

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Surgery as part of Multimodal Treatment

- Cancer Centre Review- 52 patients – 1990-2008
- 52 patients (40 female, 12 male) – 45 month f/u
- Overall – 39 had surgery; 13 non-operative
- Tamoxifen/ NSAID (all after 2001)–
  - 16 pts – 6 stable, 1 PR, 1 CR, 6 progressed -50% success
- 9 surgery alone – 78% (7/9) control
- Preoperative Chemoradiation and Surgery
  -30 patients– 90% local control rate

Francis et al Ann Surg Oncol 2009;16:1650-54

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Algorithm / Conclusion

- Trial of observation should be standard to determine the underlying growth pattern/ biology
- Hormonal therapy and anti-inflammatories may be considered early with stabilization considered a success

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Algorithm / Conclusion

- Beyond this, surgery is a key component of the **multidisciplinary care** of desmoid tumours
  - Surgery alone when feasible (...easy, although rare)
  - Avoid surgery or use surgery in a supportive fashion (i.e. facilitate RT) when not feasible or will result in major disability or disfigurement
  - As a component of multimodal treatment (reserve most aggressive treatment for more aggressive biology)

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Questions?