Sarcoma

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Objectives

Medical Expert:

1. **Etiology and epidemiology**
2. **Molecular genetics**
3. **Clinical diagnosis**
4. **Staging/Histology**
5. **Prognostic indicators/prognosis**
6. **Management of extremity and superficial trunk sarcoma**
7. **Management of retroperitoneal and visceral sarcoma**
8. **Management of distant metastatic disease, systemic treatment**
9. **Management of recurrent disease**
10. **Management of desmoid tumours**

Objectives

Collaborator:

1. **The role of neo-adjuvant and adjuvant treatment for sarcomas**

Manager:

1. **Surveillance following resection**

Scholar

Etiology and Epidemiology

- At three weeks of gestation the single layered blastula re-organizes into three layers
  - Ectoderm
  - Mesoderm
  - Endoderm

Etiology and Epidemiology

- Arise from mesenchymal cells, or mesoderm derived elements

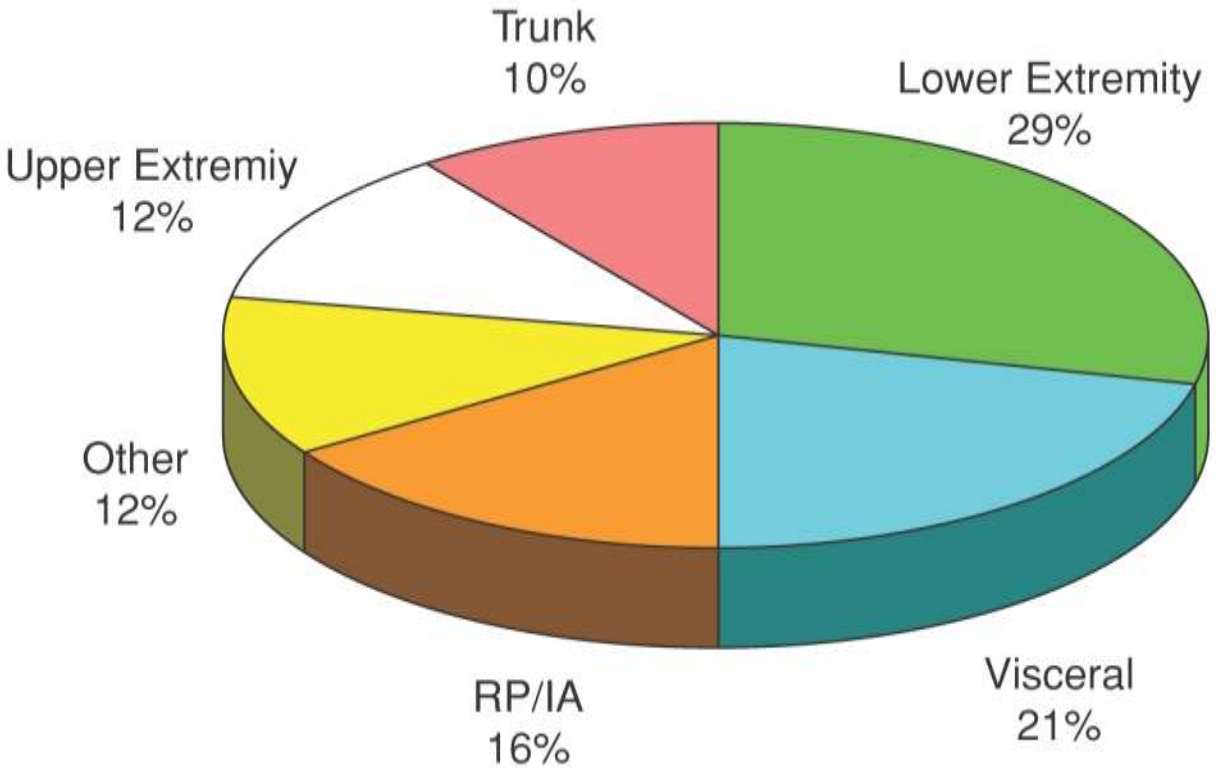
  - Muscle
  - Fat
  - Nerve/nerve sheath (derived from ectoderm)
  - Cartilage
  - Blood vessels
  - Bone

Etiology and Epidemiology

- Sarcomas are rare and account for a heterogenous group of cancers
- 12,000 new cases in the United States per year
- Represent <1% of all new cancers

Etiology and Epidemiology

- Equally distributed between males and females
- Occur in all age groups and are among the most common in children
- Most occur in the extremities or trunk
- 80% soft tissue
- 20% bone

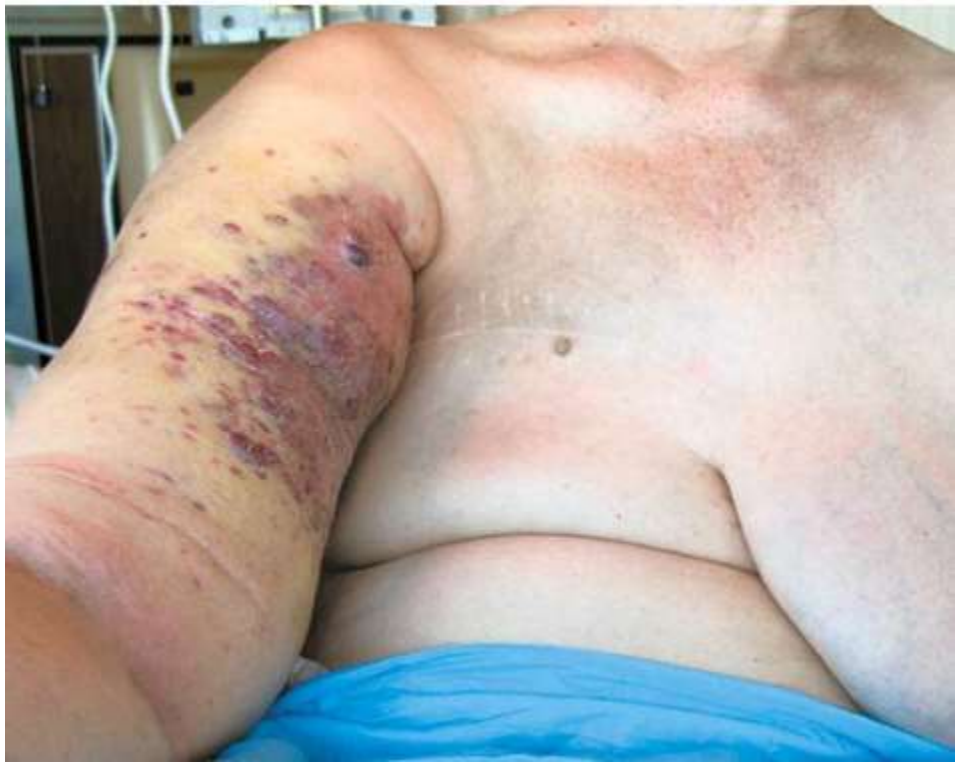


- Sarcomas are not thought to occur from the malignant degeneration of benign soft tissue tumours
- Trauma may lead to the identification of a sarcoma, but is not thought to lead to the development of a sarcoma

- Industrial chemical exposure
  - Vinyl chloride and arsenic are known to cause hepatic angiosarcoma
  - Phenoxy herbicides are thought to cause soft tissue sarcomas

- Radiation therapy
  - Recognized as a cause of sarcoma of soft tissue and bone
  - Latent period of 8 years
  - Most common soft tissue subtype is undifferentiated pleomorphic sarcoma
  - Most common subtype in women treated for breast cancer is angiosarcoma

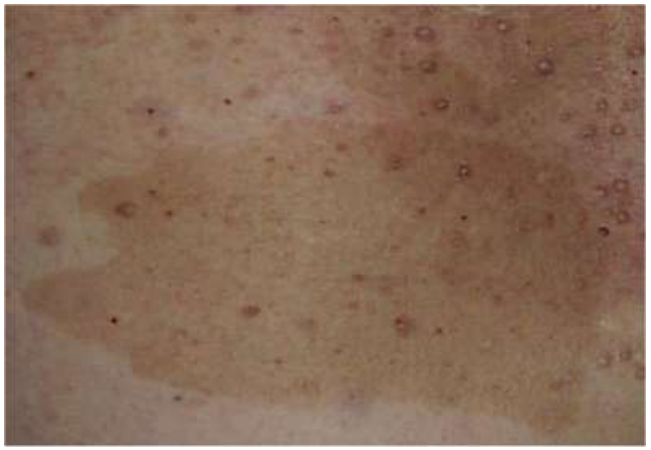
- Chronic edema
  - Lymphangiosarcomas may arise following significant and prolonged edema
  - Seen post-mastectomy (Stewart-Treves syndrome)
  - Also described with filarial infections



- Immunosuppression
  - Kaposi sarcoma was previously only seen in elderly Mediterranean men
  - Now one the opportunistic diseases associated with HIV

Genetic Predisposition

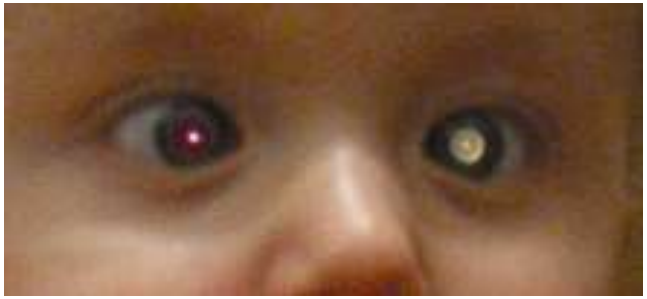
- Familial adenomatous polyposis
  - Mutations in APC gene
  - Predisposition to desmoid tumours



- Neurofibromatosis type I
  - Benign neurofibromas can undergo malignant change to malignant peripheral nerve sheath tumours
  - Rhabdomyosarcomas are also more common in NF-1

- Li-Fraumeni syndrome
  - 7% of children with soft tissue sarcomas have Li-Fraumeni syndrome
  - Germline mutation in the p53 tumour suppressor gene; autosomal dominant
  - Characterized by sarcomas, breast cancer, leukemias, brain cancer, and adrenocortical cancer at an early age

- Retinoblastoma
  - Osteosarcoma associated with the familial or bilateral type
  - Other sarcomas can also develop and is due to the mutated RB gene



Molecular Genetics

- Sarcomas can be divided into two major groups based on genetics
  - Specific genetic alterations and simple karyotypes
  - Non-specific alterations with complex, unbalanced karyotypes with numerous losses and gains

- Fusion genes
  - Represent simple karyotypes
  - Occur from chromosomal translocations and cause one third of all sarcomas
  - Protein product acts as a abnormal transcription regulator

- Inactivation of p53
  - Thought to occur in sarcomas with unbalanced and complex karyotypes
  - p53 is upregulated in cells with DNA damage and leads to cell cycle arrest and allows for DNA repair or apoptosis

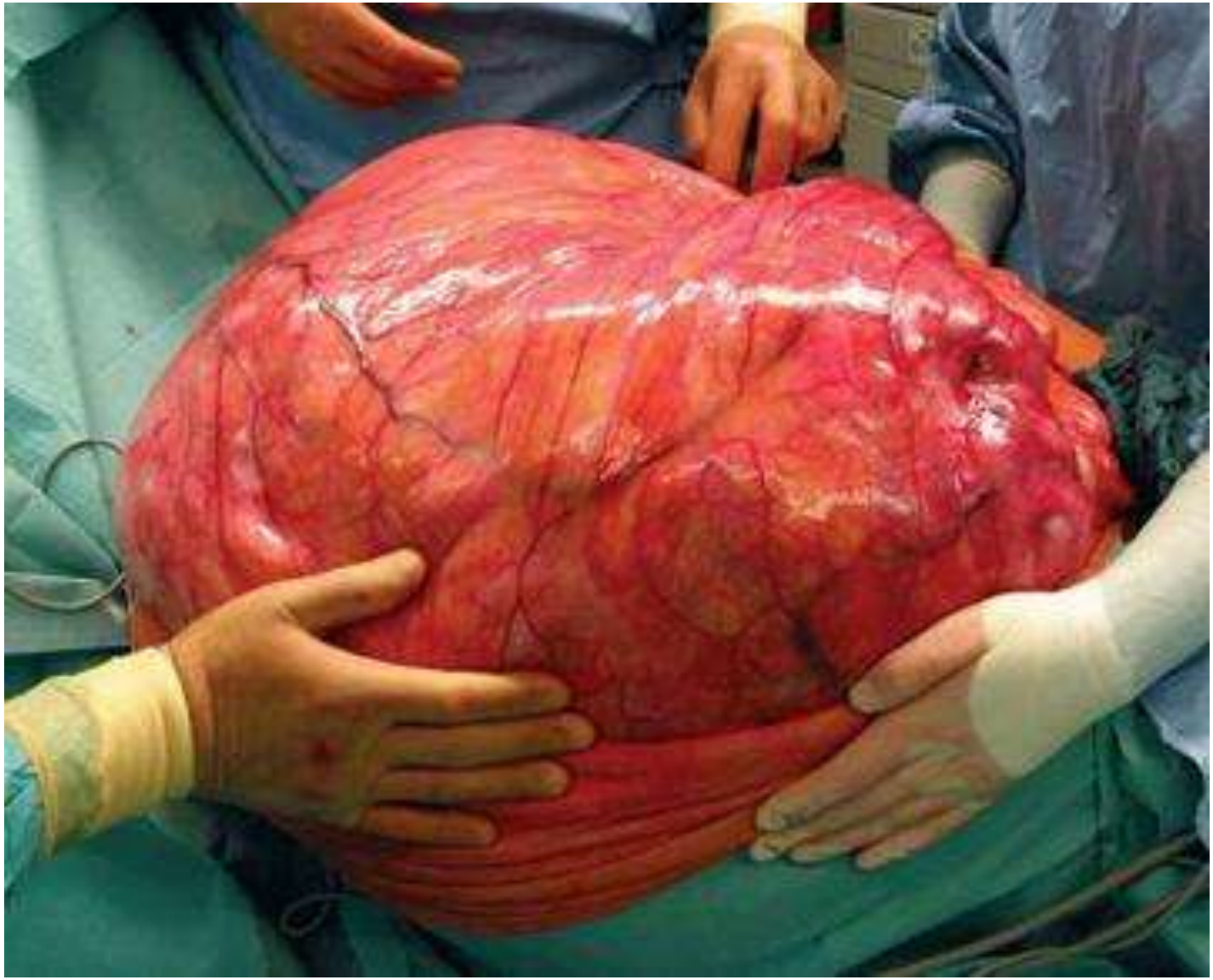
Clinical Diagnosis

- Soft tissue sarcomas
  - Usually present with an asymptomatic mass
  - Usually push other structures away rather than invade them
  - Extremity sarcomas are usually detected at a smaller size than retroperitoneal or abdominal sarcomas

Clinical Diagnosis

- Soft tissue sarcomas
  - Usually present with an asymptomatic mass
  - Usually push other structures away rather than invade them
  - May present with early satiety, abdominal fullness, or non-specific abdominal pain
  - Extremity sarcomas are usually detected at a smaller size than retroperitoneal or abdominal sarcomas

- Soft tissue sarcomas
  - Most soft tissue masses are benign
  - Concerning features
    - Large size >5 cm
    - Rapid increase in size
    - Deep location
    - Immobile
    - Recurrence after previous excision



Classification

CONNECTIVE TISSUE	BENIGN SOFT TISSUE TUMOR	MALIGNANT SOFT TISSUE TUMOR (SARCOMA)
Fat	Lipoma	Liposarcoma
Fibrous tissue	Fibroma	Fibrosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Bone	Osteoma	Osteosarcoma
Cartilage	Chondroma	Chondrosarcoma
Synovium	Synovioma	Synovial sarcoma
Blood vessels	Hemangioma Hemangiopericytoma	Angiosarcoma
Lymphatics	Lymphangioma	Lymphangiosarcoma
Nerve	Neurofibroma	Neurofibrosarcoma
Mesothelium	Benign mesothelioma	Malignant mesothelioma
Histiocytes	Benign fibrous histiocytoma	Malignant fibrous histiocytoma
Uncertain		Ewing sarcoma Alveolar soft parts tumor Epithelioid sarcoma

- Most common sarcoma types
  - GIST
  - Undifferentiated/unclassified soft tissue sarcoma
  - Liposarcoma
  - Leiomyosarcoma
  - Synovial sarcoma
  - MPNST
  - Rhabdomyosarcoma
  - Fibrosarcoma
  - Primitive neuroectodermal tumor/extraskeletal Ewing tumor
  - Angiosarcoma

- Immunohistochemistry
  - Muscle markers
    - Actin
    - Desmin
    - Myoglobin
  - Nerve sheath
    - S100 antigen
  - Synovial and epitheliod
    - Cytokeratin
  - Endothelial
    - Factor VIII

- Fluorescence in situ hybridization (FISH)
  - Translocations
- Reverse transcriptase PCR
  - Fusion genes

- Grading systems
  - Three tier
    - Well differentiated, low grade
    - Moderately differentiated
    - Poorly differentiated, high grade
  - French Federation of Cancer Centres Sarcoma Group
    - Differentiation, mitotic activity, necrosis

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension*
T1a	Superficial tumor
T1b	Deep tumor
T2	Tumor more than 5 cm in greatest dimension*
T2a	Superficial tumor
T2b	Deep tumor

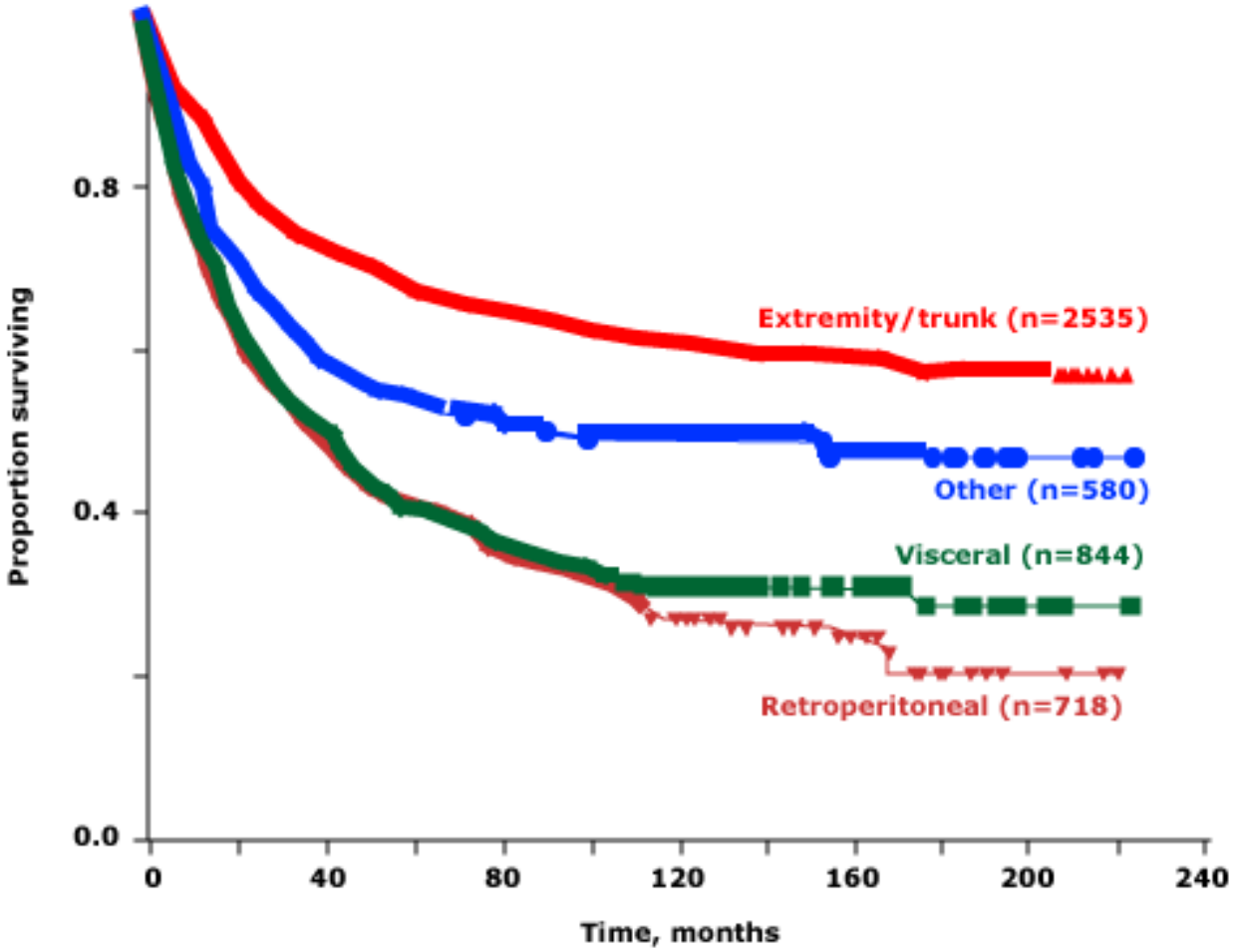
Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3

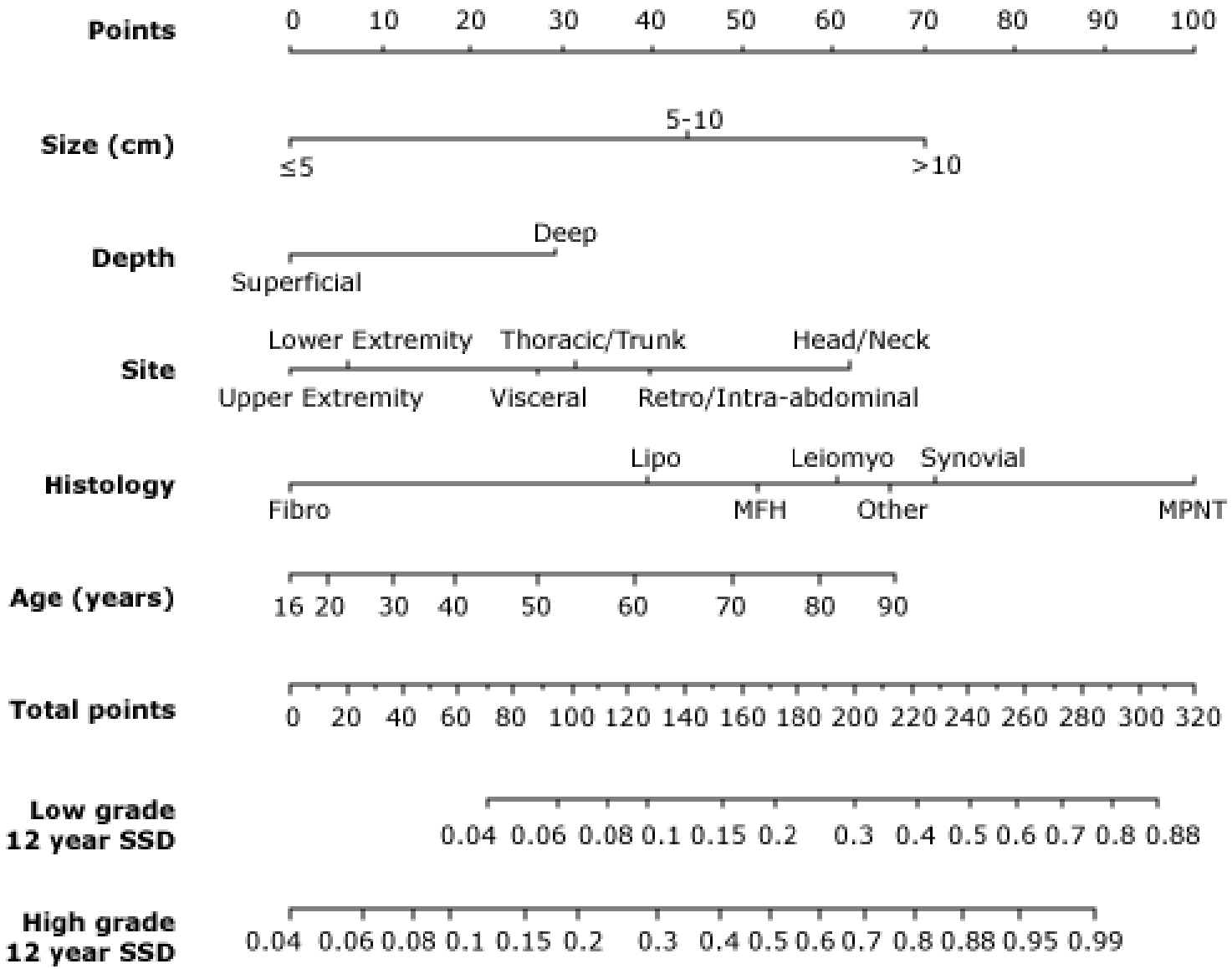
Prognostic Factors

- Stage
  - Disease free survival
    - I – 86
    - II – 72
    - III – 52
  - Overall survival
    - I – 90
    - II – 81
    - III – 56

- Grade
  - Metastases free survival
    - I – 98
    - II – 85
    - III – 64
- Tumour size and site are also independent prognostic factors


Proportion surviving
0.8
0.4
0.0
0
40
80
120
160
200
240
Time, months
Extremity/trunk (n=2535)
Other (n=580)
Visceral (n=844)
Retroperitoneal (n=718)

- MSK postoperative nomogram predicts sarcoma specific death within 12 years based on a number of prognostic factors
- Assumes that the patient does not die of another cause first


Points
0 10 20 30 40 50 60 70 80 90 100
Size (cm)
5-10
≤5
>10
Depth
Deep
Superficial
Site
Lower Extremity
Thoracic/Trunk
Head/Neck
Upper Extremity
Visceral
Retro/Intra-abdominal
Histology
Lipo
Leiomyo
Synovial
Fibro
MFH
Other
MPNT
Age (years)
16 20 30 40 50 60 70 80 90
Total points
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320
Low grade 12 year SSD
0.04 0.06 0.08 0.1 0.15 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.88
High grade 12 year SSD
0.04 0.06 0.08 0.1 0.15 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.88 0.95 0.99

Extremity and Superficial Trunk Sarcoma

- Management
  - Resection with a negative margin
    - 1 cm for fat and muscle, smaller margins acceptable for fascia
    - Peritoneal stripping should be avoided to reduce risk of radiation induced fractures
    - Nerves can be preserved by leaving the nerve sheath as a margin

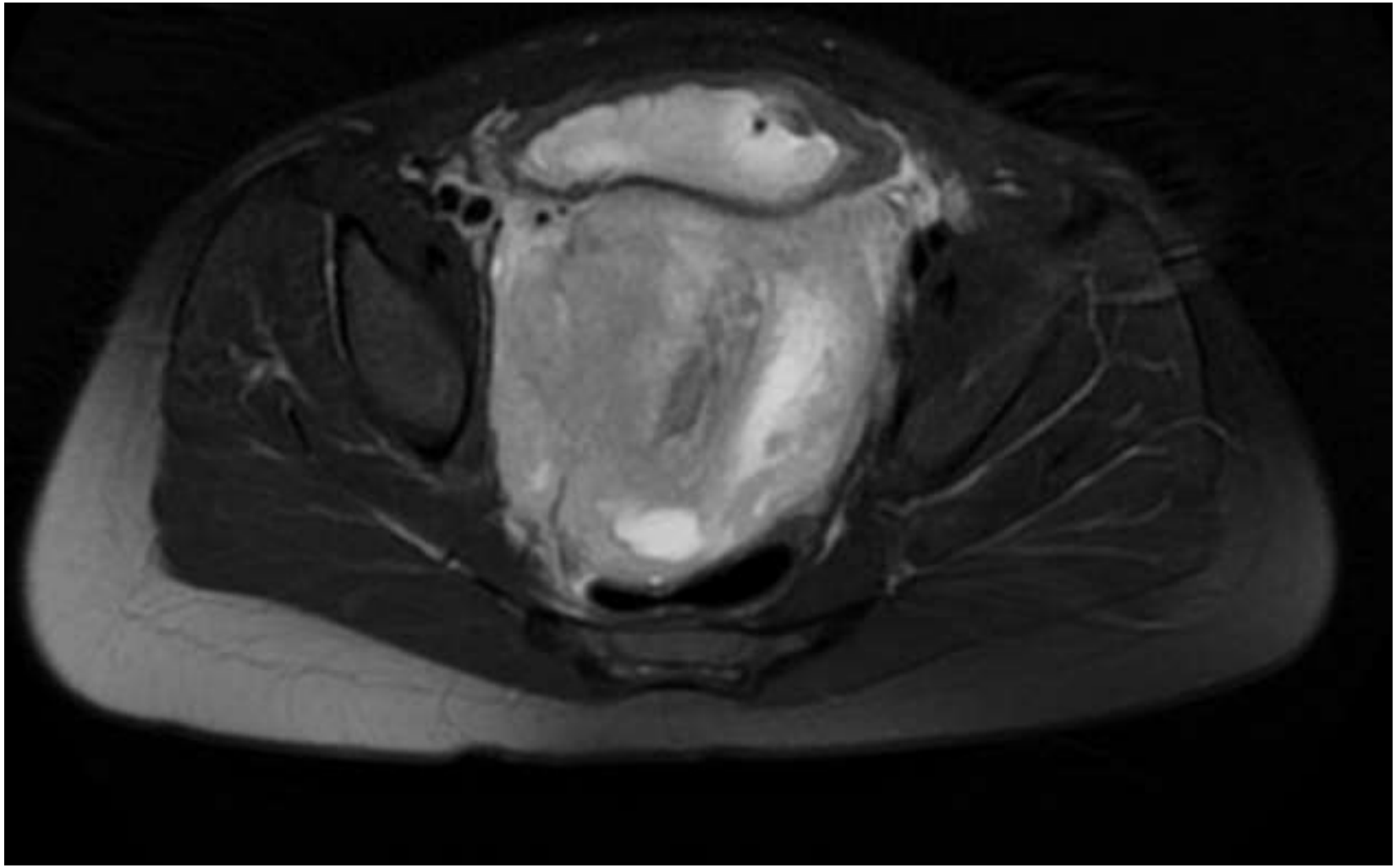
- Management
  - Radiation therapy
    - Combined with limb sparing surgery improves local recurrence rates, but not survival
    - Not required for low grade, <5cm, superficial tumours
    - May be given preoperatively or postoperatively

- Management
  - Nodal dissection required only if there is evidence of nodal involvement
  - ?SLNB

Case

- 30 month old male
  - 1 month of constipation and overflow diarrhea
  - One episode of BRBPR
  - Urinary retention and abdominal distension x4 days

- Ultrasound
  - 6x5 cm pelvic mass
- MRI



- CT Thorax
  - No evidence of metastatic disease

Retroperitoneal and Visceral Sarcoma

- Diagnosis
  - CT abdomen/pelvis to evaluate primary tumour
  - CT chest to evaluate for metastatic disease
  - MRI does not add much value
  - Percutaneous biopsy allows for a diagnosis but may not be necessary if the CT is consistent with a sarcoma and it is resectable

- Diagnosis
  - Important to assess for B symptoms (lymphoma)
  - Scrotal exam to assess for testicular cancer

- Unresectable disease
  - Extensive vascular involvement
    - Aorta, IVC, SMA, SMV
  - Peritoneal implants
  - Distant metastases
  - Spinal cord involvement

- Most common types (adult)
  - Liposarcoma
  - Leiomyosarcoma
  - Undifferentiated/unclassified sarcoma
  - MPNST
  - Rhabdomyosarcoma

- Most common types (pediatrics)
  - Extraskeletal Ewing sarcoma/primitive neuroectodermal tumour (PNET)
  - Rhabdomyosarcoma
  - Fibrosarcoma

- Management
  - Surgical resection with R0 margins is the most important prognostic factor
  - Often requires resection of adjacent organs
    - Kidney, colon, pancreas, spleen, small bowel

- Management
  - R1 resection is best managed with reresection and adjuvant radiation therapy
  - If R1 resection is anticipated, intraoperation radiation therapy should be considered, or clips left

- Management
  - Preoperative radiation therapy may be beneficial
    - Tumour displaces small bowel
    - Gross tumour volume can be defined for radiation treatment planning
    - Unresectable tumour may be converted to a resectable tumour

- Management
  - Debulking surgery has not been shown to offer a survival benefit and is not recommended

Distant Metastatic Disease

- Management
  - Most common site of metastatic disease is the lung followed by the liver
  - Systemic chemotherapy is used alone or in combination
    - Choice based on histology
  - Some patients may benefit from a metastectomy

Systemic Therapy

- Chemotherapy
  - Different regimens are used
    - Usually include doxorubicin and ifosfamide
  - Adjuvant chemotherapy is not considered to be a standard approach as there has not been a demonstrated benefit
  - Regional hyperthermia may help
    - 40 to 43 C for 60 minutes

Case

- Taken to OR for cystoscopy and bx
  - Bladder wall appeared normal
  - Biopsies taken percutaneously
    - Prostatic embryonal rhabdomyosarcoma
- Treated with neoadjuvant chemotherapy
  - vincristine, dactinomycin and cyclophosphamide

Case

- Reviewed at the Hospital for Sick Children as well as MD Anderson Cancer Centre
  - Will receive proton therapy

Recurrent Disease

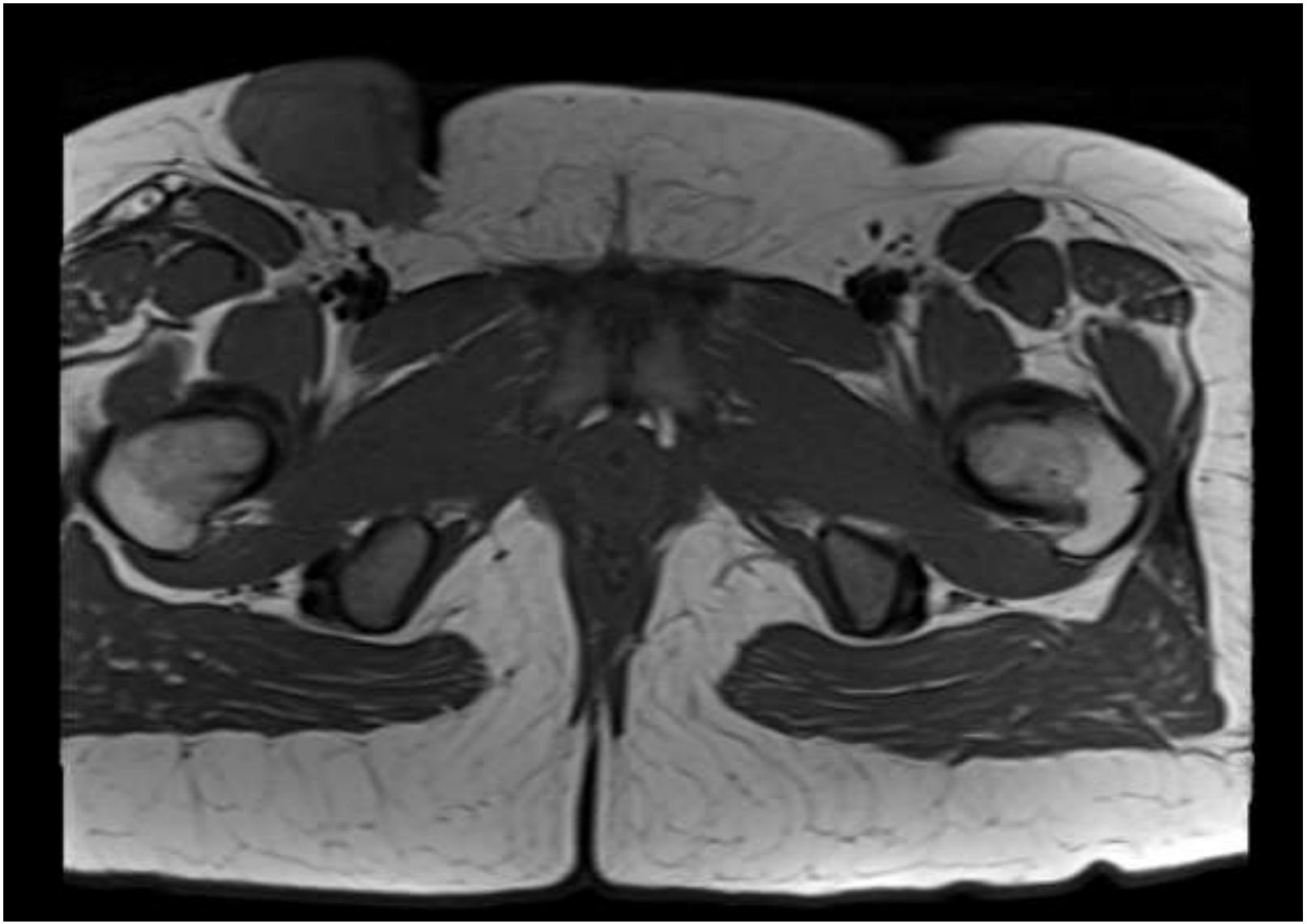
- Presentation
  - Most recurrences occur within 2 years, however they may occur at any time
  - Clinical follow up
  - CT Thorax annually for the first 2 or 3 years
  - Site specific investigations include MRI (extremity or superficial trunk) and CT (retroperitoneal)

- Management
  - Biopsy should be performed and referenced to original tumour
  - Recurrent disease should be resected if there is no evidence of metastatic disease
  - For patients initially treated with resection alone, resection and radiation should be performed

Case

- 22 y/o female who presents with firm, painless masses involving the right side of the abdomen and the right groin
- Otherwise healthy
- Underwent an excisional biopsy of one lesion

- Pathology showed fibromatosis
- Patient lost to follow up x10 months
- Increase in size of masses during that time



Desmoid Tumours

- Also known aggressive deep seated fibromatosis
- Locally aggressive, benign tumour with a high rate of recurrence after complete resection
- < 3 % of all soft tissue tumours
- Women more commonly affected
- Usually occurs between age 15 and 60

- Most arise sporadically
- 5 to 15 % associated with FAP
  - APC gene mutation
- Risk factors include family history of desmoid tumour, pregnancy, FAP, and trauma

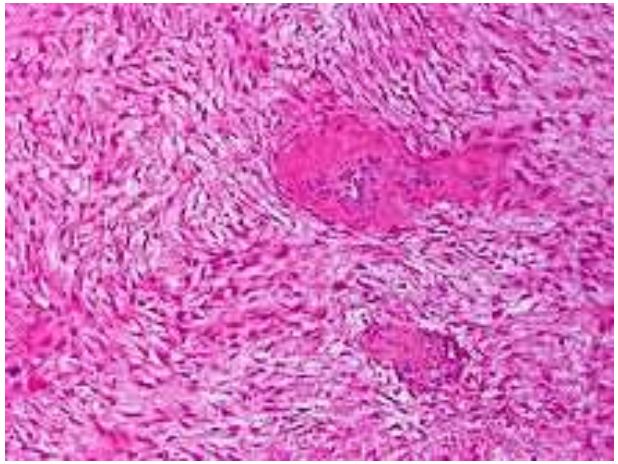
- Thought to be due to dysregulated wound healing
- APC and β-catenin mutations have been identified
  - A normal APC protein prevents accumulation of β-catenin

- Clinical presentation

  – Most common sites
    - Extremity/trunk
    - Abdominal wall
    - Intra-abdominal
  – Presents as a painless deep seated mass, or with mass effects if intra-abdominal

- Imaging
  - CT or MRI can be used to identify the relationship of the mass to adjacent structures
    - MRI may be better for extremity desmoids
  - Cannot distinguish desmoids from malignant soft tissue tumours

- Biopsy
  - Core needle or incisional
  - Cells usually stain for vimentin, actin, and β-catenin



- Staging
  - No need for staging investigations as desmoids do not metastasize
  - Colonoscopy should be considered to assess for FAP

- Management

  – Desmoid tumours have a variable clinical course
    - Remain stable
    - Regress spontaneously
    - Progress slowly or rapidly

- Management
  - Due to the potential for regression, a watch and wait approach may be used
  - Difficult to identify patients who will have regression however

- Management
  - Observation appropriate for desmoids that are potentially resectable, asymptomatic, and not causing any impairments
  - May also be appropriate where resection would lead to significant morbidity

- Management

  – Surgical resection indicated for symptomatic tumours, rapidly progressive tumours, those which pose a risk to adjacent structures, and cosmetically unacceptable tumours

- Management
  - Complete resection with negative margins
    - May necessitate a bowel resection or abdominal wall reconstruction
  - High rate of recurrence even with complete resection
  - Must plan for potential re resection

- Management
  - Radiation therapy can be used as a primary treatment modality
  - Time to regression is often long
  - May be a good option for patients who are not surgical candidates

- Management
  - Adjuvant radiation therapy can be considered in patients with large tumours or those with microscopically positive margins
  - Neo-adjuvant radiation therapy can be helpful to increase resectability and decrease recurrence – still being evaluated

- Management

  – Systemic therapy
    - Can be used for unresectable desmoids
    - Choice depends on urgency of situation
    - NSAIDs, hormonal therapy, imatinib, or cytotoxic chemotherapy can be used
      – Doxorubicin combinations
      – Vinblastine and methotrexate combinations

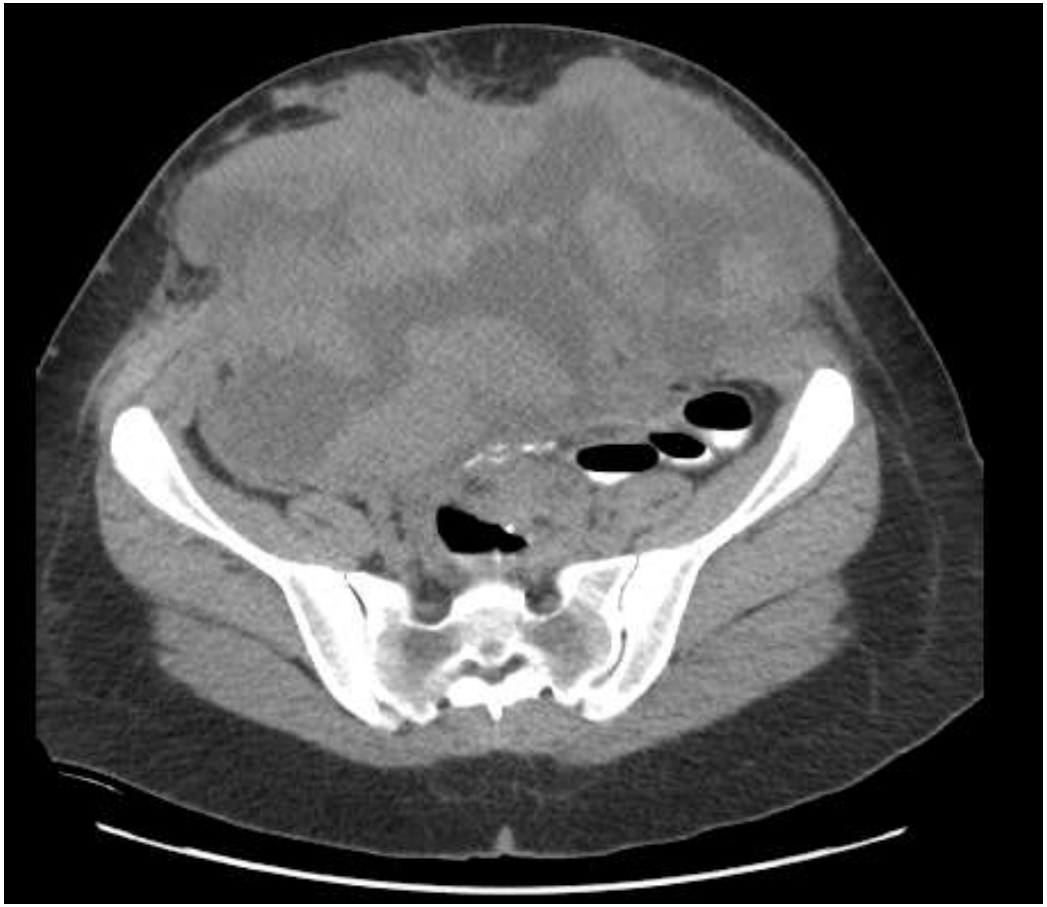
- Surveillance
  - NCCN recommends a history and physical with appropriate imaging every 3 to 6 months for two to three years, then annually

Case

- Desmoids quite large when the patient returned to clinic and involved the right side of the anterior abdominal wall and the right groin
- Due to the extensive disease and the increasing size the patient received radiation therapy

- Went for a second opinion in Toronto
  - Had a colonoscopy and was found to have FAP
  - Underwent a total abdominal proctocolectomy with diverting loop ileostomy and ileoanal pouch
  - Ileostomy was reversed

- Went on to develop intra-abdominal desmoids following this procedure



- Started on systemic therapy
  - Treated with methotrexate and vinblastine
  - Switched to docetaxel due to tumour progression
  - Stopped docetaxel due to side effects
- Currently experiencing regression of desmoids clinically and radiographically

Gastrointestinal Stromal Tumours

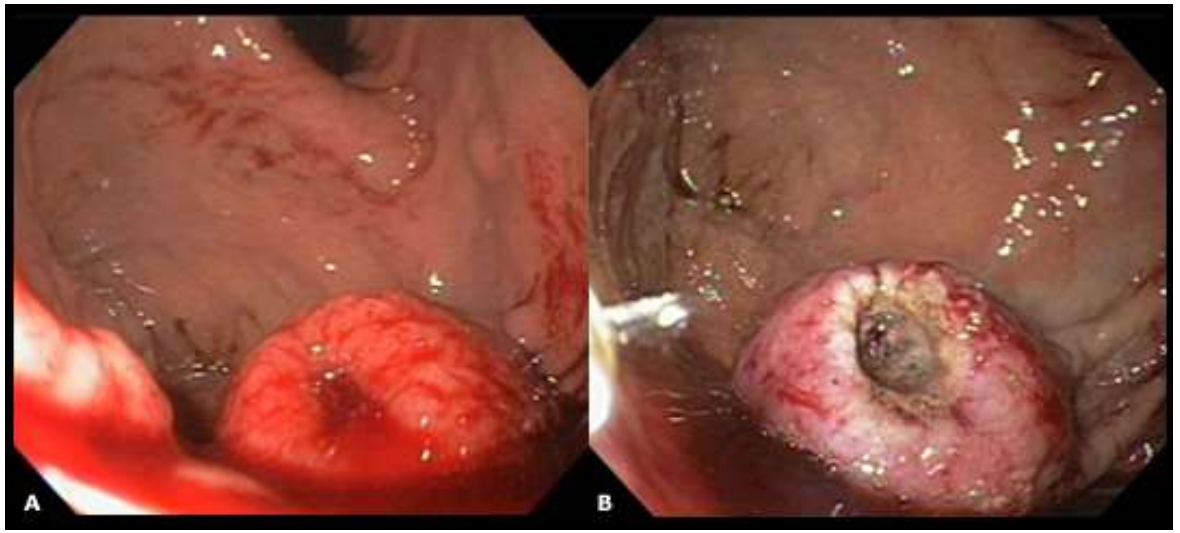
- Were previously most likely classified as leiomyosarcomas
- GISTs do not have well differentiated muscle cells however
- Originate from the interstitial cells of Cajal
  - These cells function within the autonomic nervous system of the bowel

- Overexpression of KIT (CD 117)
  - Diagnosis can be made by immunohistochemistry
  - The KIT protooncogene encodes the KIT protein which is a receptor with an intracellular tyrosine kinase domain
  - Mutations lead to ligand independent dimerization and activation of tyrosine kinase function

- Most GISTs are sporadic
- Can be associated with neurofibromatosis I

- Presentation

  – Non specific symptoms such as nausea, vomiting, or abdominal pain
  – GI bleed



- Presentation

  – Most common site
    - Stomach 50-60%
    - Small bowel 30-40%
    - Colon and rectum 5%
    - Esophagus 5%
    - Can also develop in mesentery, omentum, or retroperitoneum

- Management
  - Complete surgical resection
  - Recurrence is common
  - Nodal dissection is not indicated as GISTs rarely metastasize to nodes

- Management

  – Imatinib
    - Tyrosine kinase inhibitor
    - Results in 80% partial response or stable disease
    - First line for metastatic disease
    - May be used in a neo-adjuvant setting in order to allow resectability
    - High risk GISTs require three years of adjuvant therapy

- Management

  – High risk patients
    - Tumour > 10 cm, mitotic count > 10/50 HPFs, > 5 cm with a mitotic count >5/50 HPFs, or a ruptured tumour (SSG XVIII trial)

- Surveillance
  - History, physical, and CT scan every 3 to 6 months for 5 years, then annually
  - Metastatic disease usually involves the liver, omentum, and peritoneum

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