Retroperitoneal Sarcoma: What the Surgical Oncologist Wants to Know

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Background

- Previously thought to be one tumor type, WHO now recognizes >100 types of sarcoma, each with specific genetic foundation and tumor biology
  - Histology determines prognosis
  - Targeted therapy in development

- Soft tissue sarcomas (STS) are rare with 12K cases / yr in US:
  - 30% Extremity Sarcoma
  - 20% Visceral Sarcoma such as GIST
  - 15% Retroperitoneal (RP) Sarcoma

- The two main types of RP Sarcoma are Liposarcoma and Leiomyosarcoma

Types of Retroperitoneal Sarcoma
WHO Classification 2013

- **50% Liposarcoma**
  - WDL: Well differentiated liposarcoma
  - DDL: Dedifferentiated liposarcoma
  - Also: Myxoid, Pleomorphic, and NOS

- **20% Leiomyosarcoma (LMS) of IVC, gonadal veins or renal vessels**

- **5% Extrapleural Solitary Fibrous Tumor (SFT)**

- **Additional rarer RP Sarcomas and “soft tissue neoplasms”**
  - Malignant Peripheral Nerve Sheath Tumor (MPNST): aggressive, metastasize
  - Desmoid/Fibromatosis: true RP desmoid is rare (usually mesenteric); high rate of local recurrence
Retroperitoneal Sarcoma: Prognosis

• 75% of RP Sarcoma are low-intermediate grade

• However, RP Sarcoma has a poor prognosis due to high (70%) rate of local recurrence
  – Limited ability to get wide margins due to:
    • Location next to vital structures
    • Large size (> 10 cm) at presentation
    • Difficulty in differentiating between well-differentiated liposarcoma and normal adjacent RP fat at surgery

• Local recurrence is usually cause of death
  – 50% 5 yr local recurrence free survival (80% for extremity sarcoma)
  – 50% 5 yr disease specific survival (70% for extremity sarcoma)
RP Sarcoma: Treatment

• **Surgery with complete gross resection is MAINSTAY**
  – Difficult to assess for traditional “R0” given difficulty in accurately assessing microscopic margins in tumors that are routinely 20-30 cm in size
  – Therefore, goal is “complete gross resection” – resect tumor and RP fat, with no visible tumor left behind
    • 8 yr median survival if complete gross resection vs 1.5 yr survival if gross disease left

• **Currently very limited role for Chemotherapy and Radiation:**
  – Chemotherapy - Doxorubicin + Ifosfamide
    • For metastatic disease (along with surgery) or higher grade locally aggressive subtypes, though rarely alters extent of resection and does not change survival

  – Radiation
    • While XRT decreases local recurrence for extremity sarcomas, questionable effectiveness for RP sarcoma – Phase 3 trial being performed now by European group (EORTC)
    • When XRT is used, it is usually neoadjuvant pre-operatively (with care about small bowel exposure), as vital organs fall into resection cavity post-operatively
Debate about extent of surgical resection needed

- RP Sarcoma is often resected with minimal margins due to vital organs, with resection only of capsules and peritoneal layers
  - In comparison, extremity sarcomas typically can get 1-2 cm margin of healthy tissue

- Thus, some groups (mainly in Europe) advocate for extended “compartmental resection” (figure A below), rather than traditional resection (figure B), with en bloc removal of all adjacent organs (even if not infiltrated): often nephrectomy, colectomy, psoas myomectomy, splenectomy, and distal pancreatectomy

Image from Kirane et al J Surg Onc 2015
Since surgical margins are key, Pre-operative imaging / planning is key

- **CT Sarcoma protocol:**
  - Arterial phase through A/P to evaluate mass’s relationship to critical vessels (celiac axis, SMA, aorta)
  - Late PV phase (90 seconds) to evaluate iliac vein / IVC involvement (especially for suspected leiomyosarcoma)
  - (Can add delayed to assess ureter location)

- **Describe all parenchymal, vascular, and bowel interfaces**
  - Not enough to say “Large 20 cm RP tumor occupying majority of abdomen”
  - Important to describe location of ureter (may need preoperative stent), small bowel interface, and relationship with unresectable vascular structures: celiac axis, SMA, SMV, as well as potentially unresectable vessels: aorta, IVC
Abutting vs invading??

• Tissues typically more resistant to tumor infiltration for WDL:
  – Muscle fascia, vascular adventitia, periosteum, joint capsules, tendons

• Tissues that are less resistant and may be resected depending on predicted morbidity:
  – Colon, pancreas, kidney, spleen, psoas muscle
  – Considerations:
    • Morbidity increases with resection of > 3 organs
    • Nephrectomy results in chronic renal insufficiency in 15% of patients, which may preclude pt from subsequent clinical trials
    • Vessels can generally be freed if not encased
Liposarcoma Overview

• Epidemiology: Arise de novo in middle-late life, though occasionally after XRT

• Well Differentiated Liposarcoma (WDL):
  – 3 subtypes: Lipoma-like, Sclerosing and Inflammatory
  – Generally fatty, but often have internal septae, soft tissue, or “dirty fat” which is the sclerosing or inflammatory component (not necessarily dedifferentiated)
  – Very low risk of metastasis, 20-40% risk of local recurrence, with grade increasing with each recurrence; 20% will eventually de-differentiate

• Dedifferentiated Liposarcoma (DDL)
  – Can occur in setting of WDL, during recurrence of WDL, or de novo
  – Much more aggressive (40% survival at 5 yr), 80% locally recur by 3 yrs, and 15-30% metastasize, mainly to lungs
  – Imaging: Intensely enhancing soft tissue component with indistinct margin and peripheral fat

• Surgery with complete gross resection is goal
  – Describe vascular and parenchymal interfaces (ureter, celiac axis, SMA, SMV, aorta, IVC, kidney, pancreas, bowel)
  – Have high level of suspicion of fat – look for asymmetry, nodularity, where is true edge
Important note for biopsy – MDM2!

• Liposarcomas (WDL + DDL) have high-level amplifications of chromosome 12 mutations, including the MDM2 and CDK4 oncogenes
  – Clinical trials currently testing CDK4 inhibitor
  – MDM2 FISH amplification available at many centers
    • MDM2: 86-92% sensitivity and 74% specificity
    • Obtain core biopsies (18g) of both the soft tissue and fatty components, and send for MDM2 testing
  – For biopsy: follow projected surgical plane, however much lower rate of seeding track than extremity sarcoma
Well-differentiated Liposarcoma

**IMAGING:** CT of large right retroperitoneal mass with “dirty” fat, displacing the right kidney anteriorly. Note the broad interface with the kidney and IVC, however the aorta, SMA and SMV are separate.

**SURGERY:** Radical resection of right retroperitoneal mass, right kidney and adrenal gland, cholecystectomy, partial resection of right hemidiaphragm and psoas resection

**PATHOLOGY:** Well-differentiated Liposarcoma, lipoma-like subtype
**Sclerosing Myxoid Liposarcoma**

**IMAGING:** CT showing homogeneously enhancing 30 cm mass, isodense to muscle, with paucity of fat. Colon is displaced anteriorly, confirming RP origin. Broad interface with right kidney; thin fat plane preserved with the compressed IVC.

**Pre-op differential given:** Liposarcoma (statistically most common) vs solitary fibrous tumor (given homogeneity).

**Surgery:** Radical resection of right retroperitoneal mass and right kidney.

**Pathology:** Sclerosing Well-differentiated Liposarcoma, with small area of dedifferentiation to low grade (grade II of III) fibrosarcoma, extending to superior and medial margins.
Well-differentiated liposarcoma resected \(\rightarrow\) recurred as Dedifferentiated liposarcoma

2012: Post-op after resection of well-differentiated liposarcoma, grade 1

2013: Recurrent fat, small volume

2014: Enlarging mass: Biopsy reveals de-differentiated liposarcoma

2015: Progression despite chemotherapy
Combined Well-differentiated and Dedifferentiated Liposarcoma

**IMAGING:** CT demonstrates an avidly enhancing RP mass, displacing the bladder and small bowel anteromedially. Lobulated encapsulated fat along the right lateral aspect, suggesting combination well-differentiated / dedifferentiated liposarcoma. Tumor extension through the inguinal canal into the abdominal wall (Fig 2).

**SURGERY:** Radical resection of right retroperitoneal and pelvic sidewall sarcoma and right ureterolysis.

**PATHOLOGY:** Dedifferentiated Liposarcoma, grade 3 with well differentiated liposarcoma in the superior, anterior and posterior margins.
Dedifferentiated Liposarcoma

**IMAGING:** CT demonstrating a 21 cm heterogeneous retroperitoneal mass that encases / invades the IVC, obstructs the ureter w/ stent in place, and interfaces with the right colon, right kidney, and pancreatic head. Peripheral hazy fat with nodularity is clue towards liposarcoma (WDL/DDL combo), rather than IVC leiomyosarcoma.

**SURGERY:** En bloc resection of tumor, IVC, R colon, R kidney, R adrenal, pancreatic head, duodenum, and distal stomach

**PATHOLOGY:** Dedifferentiated liposarcoma, grade 3
Pitfall: Retroperitoneal Lipomatosis

**IMAGING:** Axial and coronal T2WI demonstrate extensive retroperitoneal fat, more prominent on the right. Given large size and RP location, well-differentiated liposarcoma was questioned. Given increasing abdominal girth, the patient favored surgery over biopsy.

**SURGERY:** Excision of retroperitoneal mass, radical right nephrectomy and adrenalectomy

**PATHOLOGY:** Mature adipose tissue, FISH negative for MDM2 gene amplification
Ddx Lipoma from WDL

- Can be difficult to distinguish large lipoma or asymmetric retroperitoneal lipomatosis from well-differentiated liposarcoma

- In a study of 301 lipomatous tumors w/ pathologic correlation, factors suggestive of well-diff liposarcoma rather than lipoma are:
  - Retroperitoneal location
  - Size > 10 cm (all RP fatty tumors < 10 cm were benign)
  - Presence of non-fatty areas
  - Age > 50
  - Recurrence


- Considerable overlap between lipoma and well-diff liposarcoma on MR, therefore often need biopsy with MDM2 testing
Leiomyosarcoma (LMS) Overview

- Tumor arising from smooth muscle, typically of uterus, extremity, or bowel, but occasionally of vessel (in RP: IVC, iliac, gonadal or renal veins)

- Tumor behavior: **METASTASIZE >>> Local recurrence**
  - Poor prognosis: 5 year survival of 35%
  - Hematogenously metastasize to lungs > liver (50% having mets by 5 yr) → stage with Chest CT
  - <5 % locally recur – do not need extended local resection

- Imaging
  - Patterns of growth: 65% extraluminal > 33% combined extra and intraluminal > 5% intravascular
  - Large heterogeneously enhancing (partially necrotic) RP mass with contiguous involvement of a vessel. Occasionally hemorrhage + Ca++
  - CT protocol: Delayed PV/IVC phase 90 sec to evaluate relationship with IVC and/or iliac veins
  - OK to biopsy despite vascular origin

- Treatment: Surgery
  - Cavectomy (Usually OK to completely resect IVC – will collateralize), primary repair / cavoplasty, or replacement with a graft
  - Chemotherapy: Relative sensitivity of LMS to chemo (30-40% sens compared to 15% for other sarcoma), therefore increasing role of chemotherapy for high-grade LMS and metastatic ds
IVC Leiomyosarcoma

IMAGING: CT: 9 cm heterogeneous mass in retroperitoneum with punctate Ca++. Initial scan in portal venous phase (A) does not delineate mass from the IVC. With delayed IVC phase ~90-110 sec (B), the mass appears to arise from the wall of the IVC, most suggestive of a leiomyosarcoma.

SURGERY: Partial IVC resection w/ bovine pericardium patch; also right nephrectomy

PATHOLOGY: IVC Leiomyosarcoma, grade 2
Left iliac vein Leiomyosarcoma

**IMAGING:** CT demonstrating a heterogeneous lobulated mass arising from the left common iliac vein, with a few thin calcifications. Coronal late venous phase shows the endo-exophytic nature of the tumor with the left common iliac vein.

**SURGERY:** Radical resection of right retroperitoneal mass, left common iliac vein resection with vein graft

**PATHOLOGY:** Iliac vein Leiomyosarcoma, grade 2
**IMAGING:** Post-contrast MRI images demonstrating an infiltrative retrocaval mass with non-occlusive bland thrombus caudal to the mass.

**SURGERY:** Excision of IVC with retroperitoneal mass, right nephrectomy, right adrenalectomy, resection of psoas muscle, crus, and diaphragm. Omentoplasty.

**PATHOLOGY:** IVC Leiomyosarcoma, grade 3 (High grade)
IVC Leiomyosarcoma with liver + lung metastases

**IMAGING:** Postcontrast MR images demonstrating a large heterogeneous mass with central necrosis, obliterating the IVC and causing right hydronephrosis. Also multiple ring-enhancing liver metastases and lung metastases.

**NOT A SURGICAL CANDIDATE** due to extent of metastatic disease

**PATHOLOGY from liver biopsy:** Leiomyosarcoma, high grade
Gonadal Vein Leiomyosarcoma

**IMAGING:** Coronal CT demonstrating large heterogeneous mass in the expected location of the left gonadal vein, with tumor thrombus extending into the left renal vein. Also, liver metastases. Axial CT image demonstrating interfaces with the left kidney, duodenum, and first jejunal branch of the SMV.

**NOT A SURGICAL CANDIDATE** due to extent of metastatic disease and SMV interface

**PATHOLOGY from liver biopsy:** Leiomyosarcoma, high grade
Solitary Fibrous Tumor (SFT) Overview

• Pathology
  – Originally thought to be of mesothelial or submesothelial origin exclusively involving the pleura, pericardium and peritoneum
  – Now considered a pathologically diverse ubiquitous neoplasm of (myo)fibroblastic origin that can originate from any site in the body, with extrapleural SFT actually more common than pleural SFT
  – “Hemangiopericytoma” no longer exists – all considered SFT

• Tumor biology
  – Most are slowly growing, low grade and benign
  – 20% with malignant features, 20% recur, 36% metastases; 5 yr survival of 85%
    • Some considered benign at resection develop metastases → need long term follow-up
  – < 5% present with hypoglycemia b/c of insulin-like growth factor “Doege Potter syndrome”

• Imaging features
  – Large hypervascular masses w/ varying degrees of central cystic/necrotic change and large vessels (flow voids)
    • Enhancement variable – some with early intense enhancement, some with delayed (due to fibrosis)
  – Serpentine vessels along periphery; rarely Ca++

• Rx: Surgical resection
Two different patients w/ similar SFT

33 yo M, incidental pelvic mass

**IMAGING:** CT demonstrates an avidly enhancing low pelvic mass w/ central hypodensity, calcification, and a small feeding vessel.

**SURGERY:** Resection of pelvic tumor

**PATHOLOGY:** Solitary fibrous tumor

50 yo F, incidental RP mass

**IMAGING:** CT demonstrates a similarly enhancing / necrotic mass in the left retroperitoneum; the lesion also had a small feeding vessel

**PATHOLOGY** from core biopsy: Solitary fibrous tumor
Large Retroperitoneal SFT in 27 yo F

**IMAGING:** MR Imaging demonstrates a markedly heterogeneous left retroperitoneal mass with mottled T2 hyperintensity and significant delayed enhancement. Pre-operatively hypothesized to be a sarcoma, vs less likely adrenal cortical carcinoma (ACC) as the adrenal gland could not be identified separately.

**SURGERY:** Radical resection of large retroperitoneal mass and left adrenalectomy

**PATHOLOGY:** Solitary Fibrous Tumor / Hemangiopericytoma (latter term no longer used)
Recurrent Solitary Fibrous Tumor after prior resection

**IMAGING:** MR imaging demonstrates a T2 hyperintense mass with progressive enhancement. PET/CT showed no significant uptake (*FDG avidity does not correlate with benign or malignant histology in SFT)

**SURGERY:** Excision of right retroperitoneal mass, right renal capsule, right adrenalectomy, right posterior sectorectomy 6/7, partial resection of right diaphragm, open cholecystectomy

**PATHOLOGY:** Malignant Solitary Fibrous Tumor
Take-Home Points

• RP Sarcomas: rare tumors
  – 50% Liposarcoma (Well-differentiated +/- dedifferentiated)
  – 20% Leiomyosarcoma of IVC or other veins
  – 5% Solitary Fibrous Tumor

• Liposarcoma: high rate of local recurrence
  – Sarcoma CT protocol w/ arterial and late venous phase
  – Report describing vascular and parenchymal interfaces, as well as ureter
  – Rx: Surgery w/ complete gross resection
  – Dedifferentiated: enhancing soft tissue component, high rate of local recurrence + metastasis
  – If unsure of Liposarcoma vs Lipoma, core biopsy for MDM2
Take-Home Points

• Leiomyosarcoma (LMS)
  – Much more likely to hematogenously metastasize (mainly to lungs) than locally recur
  – Late venous phase shows relationship to IVC, 65% are exophytic
  – Poor prognosis

• Solitary Fibrous Tumor (SFT)
  – Extrapleural SFT is more common than the pleural SFT
  – Slowly growing, usually benign; but can have delayed recurrence so need follow-up
  – Avidly enhancing masses w/ necrosis and variable enhancement pattern (intense early enhancement, or delayed enhancement w/ flow voids)
References


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