II BECA MÉDICA DE OBSERVADOR INTERNACIONAL FUNDACIÓN MARI PAZ JIMÉNEZ CASADO 2018

- **TÍTULO**: Tumores del estroma gastrointestinal (GIST): cirugía en la enfermedad metastásica e identificación de factores predictivos de respuesta. Experiencia comparada en hospital secundario español y centro de referencia internacional.

- **Objetivo:** Basándonos en la comparativa acerca de la cirugía en enfermedad oligometastásica en otro tipo de tumores gastrointestinales, como el adenocarcinoma de colon con enfermedad peritoneal o hepática, existe la práctica clínica en algunos centros como el nuestro de realizar cirugía del tumor primario en este tipo de sarcomas con enfermedad diseminada cuando cumplen ciertos criterios de estabilidad o respuesta. En base a esto, planteo un estudio retrospectivo comparando la cohorte del Hospital de Fuenlabrada con la práctica en un centro de referencia (Memorial Sloan Kettering Cancer Center) en Nueva York. Se elegirán pacientes con GIST metastásico tratados en ambos centros con y sin cirugía del primario, para comparar si de esta práctica quirúrgica subyace un aumento en supervivencia libre de progresión o global como objetivo principal. Por otro lado, se evaluarán las características clínicas de los diferentes sujetos, buscando marcadores que predigan mejor respuesta a la terapia diana.

  La idea es aprender el manejo de otros centros basado no sólo en ensayos clínicos que evalúen nuevas terapias dirigidas, si no determinados factores clínicos que puedan tener impacto en la práctica habitual y aportar supervivencia y calidad de vida a los pacientes.

MEMORIA DEL PROYECTO O PROGRAMA DE LA ROTACIÓN

♣**Introducción** (antecedentes del proyecto de investigación propuesto): Se trata de un programa de rotación externa en calidad de "observador" (*observership*) durante dos meses (Febrero y Marzo de 2019) en la unidad de Sarcomas en el Memorial Sloan Kettering Centre situado en la ciudad de Nueva York.

♣ **Objetivos del proyecto:**

-Formación en manejo de sarcomas, así como terapéutica utilizada basada en ensayos clínicos y nuevos marcadores clínicos y biológicos.

-Manejo de enfermedad oligometastásica en términos de cirugía combinada con terapias dirigidas: selección de pacientes.

-Estudio retrospectivo acerca de manejo de GIST en centro de referencia comparado con mi hospital de trabajo: identificación de posibles factores predictores de mejor respuesta o supervivencia más prolongada.

-Conseguir varias publicaciones científicas que puedan ayudar a arrojar nueva evidencia científica, y sirvan de base para generar hipótesis en futuros ensayos clínicos.

♣**Material y métodos:** Estancia dos meses (febrero y marzo de 2019) en un hospital de referencia en patología oncológica (Memorial Sloan Kettering Cancer Centre) en la unidad de sarcomas, una de las más experimentadas y exitosas en Estados Unidos, compuesta por un grupo de 5 doctores dirigidos por William Tap, incluyendo a la mayoría de los pacientes en ensayos clínicos.

El trabajo de investigación que propongo consiste en recoger a los pacientes con GIST metastásico en tratamiento, y comparar aquellos que sólo utilizan terapias diana, frente a los que incluyen cirugía en mi centro (Hospital de Fuenlabrada) y en el centro de Nueva York.

Se recogerán características clínicas de los pacientes, junto con datos de cirugía en caso afirmativo y progresión y supervivencia hasta la fecha y se compararán aquellos operados y no.

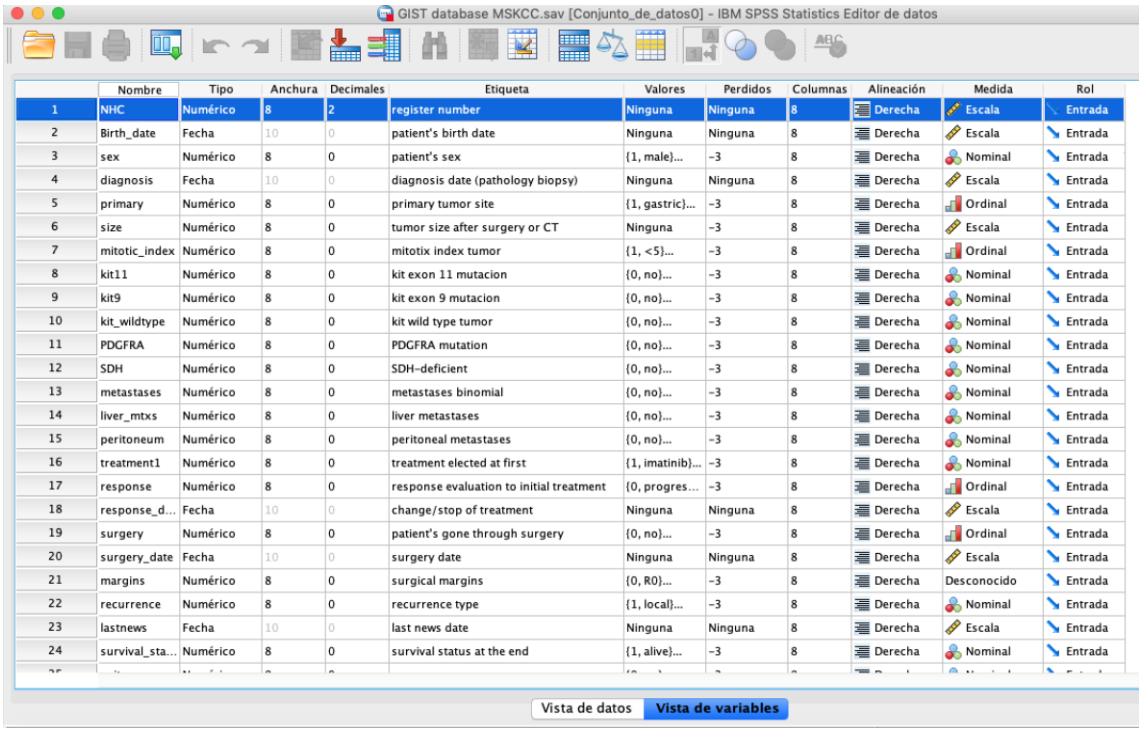
♣ **Utilidad del proyecto:**

-Aprendizaje de técnicas novedosas en tumores raros en centro de referencia.

-Consecución de publicaciones científicas que vengan a ampliar conocimiento de comunidad científica y sirva para plantear hipótesis sobre nuevos ensayos clínicos.

-Integración de trabajo multidisciplinar en distintos centros.

Base de datos del proyecto en el SPSS versión 20



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1	NHC	Numérico	8	2	register number	Ninguna	Ninguna	8	Derecha	Escala	Entrada
2	Birth_date	Fecha	10	0	patient's birth date	Ninguna	Ninguna	8	Derecha	Escala	Entrada
3	sex	Numérico	8	0	patient's sex	{1, male}...	-3	8	Derecha	Nominal	Entrada
4	diagnosis	Fecha	10	0	diagnosis date (pathology biopsy)	Ninguna	Ninguna	8	Derecha	Escala	Entrada
5	primary	Numérico	8	0	primary tumor site	{1, gastric}...	-3	8	Derecha	Ordinal	Entrada
6	size	Numérico	8	0	tumor size after surgery or CT	Ninguna	-3	8	Derecha	Escala	Entrada
7	mitotic_index	Numérico	8	0	mitotix index tumor	{1, <5}...	-3	8	Derecha	Ordinal	Entrada
8	kit11	Numérico	8	0	kit exon 11 mutacion	{0, no}...	-3	8	Derecha	Nominal	Entrada
9	kit9	Numérico	8	0	kit exon 9 mutacion	{0, no}...	-3	8	Derecha	Nominal	Entrada
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11	PDGFRA	Numérico	8	0	PDGFRA mutation	{0, no}...	-3	8	Derecha	Nominal	Entrada
12	SDH	Numérico	8	0	SDH-deficient	{0, no}...	-3	8	Derecha	Nominal	Entrada
13	metastases	Numérico	8	0	metastases binomial	{0, no}...	-3	8	Derecha	Nominal	Entrada
14	liver_mtxs	Numérico	8	0	liver metastases	{0, no}...	-3	8	Derecha	Nominal	Entrada
15	peritoneum	Numérico	8	0	peritoneal metastases	{0, no}...	-3	8	Derecha	Nominal	Entrada
16	treatment1	Numérico	8	0	treatment elected at first	{1, imatinib}...	-3	8	Derecha	Nominal	Entrada
17	response	Numérico	8	0	response evaluation to initial treatment	{0, progres...	-3	8	Derecha	Ordinal	Entrada
18	response_d...	Fecha	10	0	change/stop of treatment	Ninguna	Ninguna	8	Derecha	Escala	Entrada
19	surgery	Numérico	8	0	patient's gone through surgery	{0, no}...	-3	8	Derecha	Ordinal	Entrada
20	surgery_date	Fecha	10	0	surgery date	Ninguna	Ninguna	8	Derecha	Escala	Entrada
21	margins	Numérico	8	0	surgical margins	{0, R0}...	-3	8	Derecha	Desconocido	Entrada
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23	lastnews	Fecha	10	0	last news date	Ninguna	Ninguna	8	Derecha	Escala	Entrada
24	survival_sta...	Numérico	8	0	survival status at the end	{1, alive}...	-3	8	Derecha	Nominal	Entrada

♣ Carta evaluación de la rotación en el Memorial Sloan Ketering Cancer Center

Memorial Sloan Kettering Cancer Center

Ciara Kelly, MBBChBAO

Sarcoma Oncology Department
Department of Medicine

Juan A. Guerra
Jefe del Servicio de Oncohematología
Profesor Asociado Universidad Rey Juan Carlos
Hospital Universitario de Fuenlabrada

April 1, 2019

Dear Dr. Juan Guerra:

This is to verify that Dr. Beatriz Antón Pascual has completed her time at Memorial Sloan Kettering Cancer Center as an observer from February 4th to March 22nd, 2019. Dr. Anton Pascual observed within The Sarcoma Service in the Department of Medicine during her time here. (Please see attached for a copy of her schedule).

This opportunity allowed Dr. Antón Pascual to develop and benefit from observing different outpatient clinics (Including rotations in our Immunotherapy and Developmental Therapeutic Clinics), as well as attending various weekly research and multi-disciplinary departmental conferences. It was our pleasure to have Dr. Antón Pascual with us for the last two months. She is a highly motivated, and enthusiastic oncology trainee. She worked well with our team and patients alike. She is a credit to your oncology training system and we wish he well in her future career.

Please let us know if you require any additional information 646 888 4312.

Sincerely,

Ciara Kelly, MBBChBAO
Memorial Sloan Kettering Cancer Center
Assistant Attending/Medical Oncology

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NCI-designated Comprehensive Cancer Center

♣ Sesión formativa para el Memorial Sloan Keterring Cancer Center

Soft tissue clasiffication

General Type	Benign Entity	Malignant Entity
Fibrous Producing	**Benign Fibrous**	**Malignant Fibrous**
(Fibrous Tissue Producing)	Calcifying Aponeurotic Fibroma Dermatofibrosarcoma Protuberans (DFSP) Desmoplastic Fibroblastoma (Collagenous Fibroma) Elastofibroma Fibromatosis • Adult Fibromatosis • Infantile Fibromatosis • Hyaline fibromatosis Fibroma of Tendon Sheath Fibrous Hamartoma of Infancy Infantile Digital Fibromatosis (Inclusion Body Fibromatosis) Myofibroma Solitary Fibrous Tumor	Fibrosarcoma • Grade 1 (Low Grade) • Grade 2 (Intermediate) • Grade 3 (High Grade) Malignant Fibrous Histiocytoma (MFH) (aka: Myxoid Fibrosarcoma) Low Grade Fibromyxoid Sarcoma Infantile Fibrosarcoma Myofibrosarcoma
Fat Producing	**Benign Fatty**	**Malignant Fatty**
	Lipoma Angiolipoma Hibernoma Lipoblastoma	Liposarcoma (LS) Well Differentiated LS Myxoid Liposarcoma Round Cell Liposarcoma Pleomorphic Liposarcoma Dedifferentiated LS
Muscle Origin	**Benign Muscle**	**Malignant Muscle**
	Leiomyoma Rhabdomyoma	Leiomyosarcoma Rhabdomyosarcoma
Vascular Origin	**Beningn Vascular**	**Malignant Vascular**

(Blood Vessel Origin)	Hemangioma Lymphangioma Glomus Tumor Kaposiform Hemangio-endothelioma	Hemangioendothelioma Hemangiopericytoma Angiosarcoma Infantile Hemangiopericytoma
Osseous Producing	**Benign Osseous**	**Malignant Osseous**
(Bone Producing) (Osteoid Producing)	Myositis Ossificans Ossifying Fibromyxoid Tumor	Osteosarcoma (OS) (Extraskeletal Osteosarcoma)
Cartilage Producing	**Benign Chondroid**	**Malignant Chondroid**
(Chondriod Producing)	Extraskeletal Chondroma	Chondrosarcoma (Extraskeletal) Myxoid Chondrosarcoma Mesenchymal Chondrosarcoma
Small Round Blue Cell	**Benign Small Round Blue Cell**	**Malignant Small Round Blue Cell**
(These tumors do not produce matrix; Non Matrix Producing)		Ewing Sarcoma / PNET (Extraskeletal Ewing Sarcoma) Rhabdomyosarcoma (specific varieties) Desmoplastic Small Round Blue Cell Tumor Lymphoma
Giant Cell	**Benign Giant Cell**	**Malignant Giant Cell**
(rare in soft tissues)	Giant Cell Tumor (GCT) Aneurysmal Bone Cyst (ABC)	Malignant Giant Cell Tumor
Neurogenic	**Benign Nervous**	**Malignant Nervous**
(Nerve origin; Very rare to occur in bone)	Schwannoma (aka: Neurilemoma) Ancient Schwannoma Neurofibroma Intraneural Ganglion Cyst Intraneural Lipoma	Malignant Peripheral Nerve-Sheath Tumor (MPNST) (aka: Neurofibrosarcoma)
Synovial/Intraarticular (Joint Related)	**Benign Synovial**	**Malignant Synovial**

	Ganglion Fibroma of Tendon Sheath Giant Cell Tumor of Tendon-Sheath (GCT of Tendon Sheath) Pigmented Villonodular Synovitis (PVNS) Synovial Chondromatosis Synovial Hemangioma Synovial Lipoma Synovial Fibroma	Malignant PVNS Synovial Chondrosarcoma Synovial Liposarcoma
Miscellaneous Origin/ Unknown Origin	**Benign**	**Malignant**
	Granular Cell Tumor Myxoma	Alveolar Soft Parts Sarcoma Clear Cell Sarcoma (Melanoma of Soft Parts) Desmoplastic Small Cell Tumor Epithelioid Sarcoma Inflammatory Myxohyaline- Tumor of Distal Extremities Synovial Sarcoma

LIPOSARCOMA – General Overview

Soft tissue sarcoma, 5,000 new cases annually. Accounts for <20% of all soft tissue sarcomas, average age at presentation 50 yrs. Occurs in the deep soft tissue of extremities most common)and retroperitoneum (20% of all mesenchymal tumors) Large bulky tumors w/multiple satellite lesions Retroperitoneal tumors may present with weight loss, emaciation, abdominal pain. May have kidney failure d/t tumor location/size.

Liposarcoma is a malignant mesenchymal neoplasm composed of lipogenic tissue with varying degrees of atypia. Liposarcoma is one of the most commonly diagnosed soft tissue sarcomas, accounting for approximately 12.8% of all sarcomas.

MRI is nonspecific except for well-differentiated tumors in which fat signal is easily distinguished, except for well-differentiated tumors in which fat signal is easily distinguished

Histological patterns:

Well differentiated -40%, Round cell/myxoid-30%, Pleomorphic-15%, Dedifferentiated Liposarcoma-5%

TX: Surgery, chemotherapy

DEDIFFERENTIATED LIPOSARCOMA (DDLPS)

Dedifferentiated liposarcoma is the least common subtype of liposarcoma and usually arises from a well-differentiated liposarcoma (WDLPS). Progression occurs in 17 % of patients when WDLPS is located in the retroperitoneum and 6% of cases when WDLPS is located in the extremities.
Dedifferentiated liposarcoma has also been defined as an atypical liposarcoma that progresses or changes over course of time with variable histologic grade. This is essentially a low grade liposarcoma admixed with a high grade spindle cell sarcoma.

These tumors occur mostly in adults and tend to grow more aggressively than a low grade well differentiated liposarcoma. They arise most commonly in the retroperitoneum.

Clinical Presentation:

• 18 % of Liposarcomas
• Most commonly occurs in patients over 50 years old
• No gender predilection
• Commonly on deep soft tissue of retroperitoneum and proximal extremities
• Progresses from WDLPS and their presentation is more frequent after a recurrence of WDLPS.
• Up to 17% of well differentiated LPS progresses to DDLPS

Signs/symptoms

• Painless enlarging mass
• Can attain a very large size
• More locally aggressive than WDLPS.
• Metastasis rate, range from 13% to 47%

Prevalence

• No gender prevalence

Age

• Most cases are diagnosed in the 6th decade of life
• Rare in children.

Sites

• Retroperitoneum
• Lower extremities
• Upper extremity
• Trunk

Biological behavior

• Up to 17% of WDLPS progress to DDLPS

• Between 13 to 47 % of patients present with metastases.

• DDLPS has 54-64% of overall survival

• DDLPS has 66 to 89% of disease-specific survival

• Location and mitotic count are the most important prognosis factors.

• Progression to dedifferentiated LPS occurs in 17% of the retroperitoneal WDLPS and 6% for the WDLPS in the extremities.

• Retroperitoneal WDLPS tend to progress more frequently to DDLPS.

Treatment

• The most reliable means of obtaining local tumor control is by wide surgical excision. In cases of positive margins re-resections should be considered option whenever possible.

• Adjuvant radiation therapy is recommended in patients with smaller margins <10 mm after the surgical resection.

Chemotherapy Regimes:

First Line	**AIM** (Adriamycin (doxorubicin)/Ifosfamide/Mesna)
Second Line	Gemcitibine/Docetaxel
	Doxorubicin/Olaratumab (phase III MSK negative)
	Palbociclib (Ibrance) - (CDK4 inhibitor)
Third Line	Eribulin
	Trabectedin
	Ifosfamide
	Clinical Trials

WELL DIFFERENTIATED LIPOSARCOMA (WDLPS)

Well-differentiated liposarcoma is the most common subtype of liposarcoma. These tumors nearly always occur in adults and have no gender predilection. They arise most commonly in the deep soft tissues of the proximal extremities (Thigh) and the retroperitoneum. Occasionally retroperitoneal liposarcomas may present as groin masses because of local extension into the peritoneal-lined scrotal sac and therefore may simulate a groin hernia

Well-differentiated liposarcoma is commonly referred to as an atypical lipoma or low grade liposarcoma.

Clinical Presentation

Rare; 2 per 1,000,000

- Most commonly presents in patients over 50 years old
- No gender predilection
- Commonly on deep soft tissue of proximal extremities and retroperitoneum
- Grows slowly
- Always deep and never subcutaneous location
- Do not metastasize
- Can dedifferentiate into a dedifferentiated liposarcoma (develop a high grade spindle cell component)

Signs/symptoms

- Painless enlarging mass
- Can attain a very large size
- Locally Aggressive
- Nonmetastatic tumor

Prevalence

- No gender prevalence

Age

- Most cases are diagnosed in the 6th decade.
- One of the most common soft tissue sarcomas
- Rare in children.

Sites

- Lower extremities (50%)

• Thigh is most common site
• Retroperitoneum (20%–33%)
• Upper extremity (14%)
• Trunk (12%)

Radiographic Presentation
Slow growth
• Variable sizes, normally more than 10 cms.
• Thick internal septations
• Deep location usually intermuscular

CT
Patterns based on amount and distribution of fat:
1. solid - attenuation > + 20 HU
2. mixed - areas of < -20 HU and areas of > + 20 HU
3. pseudocystic - homogenous density between – 20 and + 20 HU

CT findings favoring a liposarcoma from a lipoma include
• poor definition of adjacent structures
• nonhomogeneous attenuation, with evidence of significant amounts of soft-tissue within the fatty mass

Microscopic Pathology
• Often with a prominent fibrous component
• The fat cells are often different sizes and shapes
• Genetic marker and ring chromosomes (12q13-15)
• Overexpression of oncogenes MDM2 and CDK4 (positive IHC for those markers).

Prognosis
Biological behavior • Slow growth
• WDLPS on extremities have shown 95% of disease-specific survival
• WDLPS on retroperitoneum had an 87% of disease-specific survival
• Location and margins are the most important prognosis factors.
• Generally never metastasize
• Progression to dedifferentiated LPS occurs in 17% of the retroperitoneal WDLPS in the retroperitoneum and 6% for the WDLPS in the extremities.
• Local recurrence rate depends on size and exact location; 13-46% for WDLPS in the extremities and 91% for the retroperitoneal cases.

Treatment

• Surgery is the mainstay of treatment. The most reliable means of obtaining local tumor control is by surgical excision with a wide excision if possible however most are marginally excised.
• Adjuvant radiation therapy is not recommended in patients with WDLS. It is generally not radiosensitive and has a less than 1% risk of distant metastasis. The benefit of radiation does not outweigh the risk
• Chemotherapy has little role in WDLS. It is a low grade tumor. These tumors are often resistant to standard cytotoxic chemotherapies, and no survival benefit derived from adjuvant chemotherapy have been published.

Chemotherapy Regimes:
First Line Palbociclib (Ibrance) - (CDK4 inhibitor)

MYXOID (ROUND CELL) LIPOSARCOMA (MLPS)

Myxoid Liposarcoma (MLPS) is the second most common group of adipocytic/lipogenic sarcomas accounting for approximately 35% of all liposarcomas. It is a malignant tumor histologically characterized by a round to oval mesenchymal cells, small signet ring lipoblasts, and rich network of capillaries in a myxoid stroma. Both myxoid and round cell liposarcomas have the same genetic translocation. It is believed that these two entities are intimately related and represent a spectrum of the disease with the theory that myxoid liposarcomas can transgress into round cell liposarcoma which is a more aggressive neoplasm with much greater potential for metastasizing. Round cell liposarcomas appear similar to a myxoid liposarcoma excpt that myxoid stroma is not present.

These tumors nearly always occur in adults but can present in younger aged population more frequently than the other types of liposarcomas. There is no gender predilection. They arise most commonly in the deep soft tissues of the proximal extremities and the retroperiteneum.

Signs/Symptoms:
Rapidly enlarging, painless mass. 30% of patient may have dull aching pain/tenderness. Some patients report trauma in the affected area and a misdiagnosis may occur ie; hematoma, muscle strain.

Prevalence:

- Male (70%)
- More frequent in Caucasian population

Age:

- Most cases occur between 50-70 years

Sites:

- Lower extremity -50%, most commonly arises in the thigh
- Upper extremity -25%
- Retroperitoneum -15%
- Head/neck -5%

- Variable sizes, may reach more than 15cm

Radiographic Presentation

- Low signal on T1 weighted images. Usually adipose tissue composes less than 10% of the tumor and is difficult to detect on an MRI as high signal on T1W images. Marked high signal on T@ weighted images, the myxoid/mucinous tissue consists of mucopolysaccharides that holds onto water and shows up on high signal T2W images.

Pathology:

- 75% of myxoid liposarcomas are associated with a chromosomal translocation t(12;16) q(13;p11)

Prognosis:

- MLPS have shown 69-100% DFS
- High risk of local recurrence (7-28%)
- 1 in 3 patients present with metastases and often occurs in unusual sites before metastasizing to the lungs such as: soft tissue (retroperitoneum, opposite extremity, axilla), bone/spine,
- Important prognostic factors are age and presence of Round cell component
- The presence of hypercellularity or round cell differentiation is associated with worsening of prognosis and higher rate of metastases
- The prognosis for multifocal myxoid liposarcoma is always poor

Treatment:

- Surgery
- Adjuvant therapy (chemo/X-RT)

Chemotherapy Regimes:

First Line	AIM (Adriamycin (doxorubicin)/Ifosfamide/Mesna)
Second Line	
	Doxorubicin/Olaratumab
	Palbociclib (Ibrance) - (CDK4 inhibitor)
Third Line	
	Trabectedin
	Ifosfamide

Clinical Trials

Pleomorphic Sarcoma

Pleomorphic sarcoma is a high-grade sarcoma of lipogenic (fatty/adipose) origin. It is a type of liposarcoma that has some lipoblasts admixed with mostly high-grade pleomorphic appearing spindle cells.

Prevalence

Represents 5 to 10% of all liposarcomas
No predilection for any race or sex
Usually affects patients between the fifth to seventh decade
Rare in younger ages
Associated with post radiation treatment in neurofibromatosis.

Signs/Symptoms

Large mass
Slowly growing tumor
Usually painless

Site

Most commonly intramuscular or in other deep sites
Occasionally occurs in subcutaneous tissue

Radiographic Presentation

- **Plain x-ray**
  No specific radiological features
  May reveal a soft tissue mass

  CT
  Often heterogenous with density similar to muscle

  MRI
  Strong enhancement post gadolinium (suggestive of malignant process)
  Usually it is very difficult to detect any fat within the mass on an MRI

Pathology

Immunohistochemstry

Vimentin
S100
Smooth muscle actin
CD34

Keratin

Desmin

Prognosis

- **Biological Behavior**

  High risk for local recurrence (wide excision option for treatment)

  High risk for metastasis

  Less than 60% survival over 5 years

  Poor prognostic factors:

  >60 yo

  Truncal location

  Deep to fascia

  Larger than 5 cm

  Vascular invasion

  Incomplete excision

Treatment

Radiotherapy and chemotherapy

Chemotherapy Regimes:

Angiosarcoma

Angiosarcoma is a rare malignant neoplasm that arises from endothelial cells of blood vessels. Very rare in infant and young adults but has a very poor prognosis. It most typically arises in the setting of chronic lymphedema often caused by radiation and /or radical lymph node dissection for breast CANCER. Characterized by an atypical, multilayered or solid endothelial proliferation and vasoformative architecture. Can occur in the skin as well as in the deep soft tissue and very rarely as a nerve sheath neoplasm. It can also rarely arise from bone.

Presentation

- Early diagnosis is usually difficult
- May be confused with a benign tumor or hematoma
- Angiosarcomas can resemble melanoma or carcinomas histologically
- Risk factors for developing an angiosarcoma:
    - Chronic lymphedema
    - Radiation
    - Sun exposure

- Nodal metastases up to 14%, but also can metastases to lung, liver and bone

Signs/Symptoms
Appear cutaneously as blue-red skin lesion
Rapidly growing painless mass

Prevalence
Extremely rare, comprise a very small portion of all sarcomas
No predilection for sex or race
Occurs most often in elderly individuals and in breast cancer patients with chronic lymphedema and radiation

Sites
The skin and soft tissue angiosarcomas are most often found in the head and neck region as well as in a lymphadematous limb
May also occur in the abdominal cavity and as a nerve sheath neoplasm
Angiosarcomas may occur in the liver

Radiographic Presentation

Plain x-ray
- No specific radiological features (demonstrate soft tissue mass)
- Calcifications are rare

MRI
- Gold standard for imaging
- Intermediate signal isointense to skeletal muscle on T1W
- Heterogenous on T2W
- Heterogenous enhancement after gadolinium
- May have significant necrosis
- Tumors with extensive necrosis may appear similar to a hematoma

Pathology

Microscopic

• Well-differentiated tumors
    • Characterized by entothelial cells with
    • Cytologic pleomorphism
        • Nuclear atypia
        • Mitotic activity
        • Multilayering, often with tufts or papillae
        • Poorly differentiated tumors
    • Endothelial cells are more atypical, close-packed, and often spindle-shaped
    • Progressive loss of evident vascular channels

Immunohistochemistry

• Factor 8 related protein
• CD31
• CD34
• Ki-67
• FLI-1
• VEGFR-3 (variable)
• Keratin

Prognosis

Biological Behavior

• Very aggressive tumor
• Often preceded by lymphedema
    • Also resulting from radiation • Prognosis depends on several factors:
    • Depth • Size (>5 cm are associated with 5-15% survival at 5 years)
    • Grade
    • Lymphovascular invasion with tumor thrombi (negative prognosis)
    • Tumors can be quite large, exceeding 5 cm in diameter
    • Metastasis rate is high, as is the death rate
    • Usual metastatic sites
    • Skin and soft tissue
    • Lung • Lymph nodes • Liver • Bone
    • There is also a tendency for satellite spreading
    • Locoregional metastasis----->surgery may be ineffective

Treatment

• Wide and deep excision
    • Positive margins are associated with high local recurrence rates

• Radiation indicated after resection; however, some patients previously treated with radiation may not be candidates for more radiotherapy

• Amputation for unresectable angiosarcomas or those that cannot be resected with wide margin and are not candidates for more radiation.

• Chemotherapy (Indicated if more than 5 cm; each patient should be considered individually)

Chemotherapy Regimes:

IV vs. Oral

IV	Liposomal doxorubicin
	Gemcitibine/Docetaxel
	Paclitaxel
Oral	Sorafenib (TKI)
	Pazopanib (TKI)

Desmoid –NEED TO ADD DATA HERE

First Line Sorafenib (TKI)

Second Line Doxil (Liposomal Doxorubicin)

Malignant Fibrous Histiocytoma (MFH; Undifferentiated Pleomorphic Sarcoma UPS)

Malignant Fibrous Histiocytoma (MFH) was first described in the 1960s presumably derived from a mixed histiocytic and fibroblastic cellular origin but is it now believed that it is a lesion derived from fibroblast differentiation. It is a malignant neoplasm (sarcoma) of mesenchymal/spindle origin. It is a high grade sarcoma with a strong potential for metastatic disease. Since the beginning MFH was recognized as a heterogeneous group of tumors with varying histology affecting both genders and all ages. Since 1978, MFH it was identified as the most common soft tissue sarcoma after Weiss and Enzinger published the first large series of tumors with those characteristics.

Four different sub-types have been described:

- Storiform-pleomorphic
- Myxoid
- Giant cell and Inflammatory

It is now often referred to as Undifferentiated Pleomorphic Sarcoma (UPS)

Of these, the storiform-pleomorphic is the most common type, accounting for up to 70% of the cases. The myxoid variant is the second most common accounting for approximately 20% of cases. After 2002 The World health Organization suggested replacing the term MFH with Undifferentited high-grade pleomorphic sarcoma (UPS). Myxoid MFH is now myxofibrosarcoma. Giant cell MFH and inflammatory MFH are now called UPS with giant cells and UPS pleomorphic sarcoma with prominent inflammation, respectively.

Clinical Data

Comprises 20% - 30% of soft tissue sarcomas
Second most common type of soft tissue sarcoma
Most commonly arises from the soft tissues but may arise from bone.
Most common soft-tissue sarcoma in adults though it can appear at any age.

Very rare in patients < 20 year old.
Most common sarcoma after radiation.
Heterogeneous tumor in histology and prognosis
Early osseous invasion and metastases to regional lymph nodes may occur

Signs/Symptoms

Rapidly enlarging, painless mass. 30% of patients may have dull aching pain or tenderness.
Some patients report trauma in the affected area (trauma does not cause MFH) and the MFH may be misconstrued as a hematoma or muscle strain
Systemic symptoms are not expected.

Prevalence

Male predilection (70%)
More frequent in Caucasian population

Age

Most cases occur between 50 and 70 years old.
Extremely rear in children.

Sites

Lower extremity 50%

Most commonly arises in the thigh
Upper Extremity 25%
Retroperitoneum 15%
Head/neck 5%

Radiographic Presentation

Deep intramuscular soft mass
Average size of 5 to 10 cm
Heterogeneous mass
Osseous involvement is frequent
Regions of mineralization may be demonstrated on plain x-rays but is unusual for an MFH
In some cases, MFH can be more aggressive and invade an adjacent bone.

Plain x-ray

Demonstrate a soft tissue mass density.
Curvilinear or punctate mineralization may be observed in 5 to 20% of patients.
Heterotopic bone formation may rarely be present along the periphery of the mass.
It is not the ideal method of study in cases of MFH.

CT scan
Nonspecific, large, soft tissue mass of predominantly muscle density, with nodular and peripheral enhancement of solid portions.
Central areas of low attenuation reflecting necrosis, hemorrhage or myxoid regions.
Fat attenuation is not observed.

MRI
Typically reveals an intramuscular mass with heterogeneous signal intensity reflecting variable amounts of collagen, myxoid tissue, necrosis, and hemorrhage.
Low to intermediate signal intensity on T1-weighted.
Intermediate to high signal on T2-weighted
Viable areas enhance with contrast
Low intensity in T1-weighted and high density in T2- weighted reflecting high water content
Areas with prominent fibroid tissue demonstrate low density in T1 and T2 weighted images.
Regions of hemorrhage have high signal on T1 and T2 weighted images.
Necrosis have similar pattern as fluid

Prognosis

Biological behavior
Metastases (35% to 45% of patients)
Lung (90%)
Bone (8%)
Liver (1%)
Lymph Nodes (1%)
Prognosis: 5 years survival overall 65%

Treatment

Wide surgical resection and postoperative radiation whenever feasible
Amputation for unresectable tumors.
Attention is directed to ruling out metastases to the regional lymph nod

Chemotherapy Regimes:

Metastatic	Doxorubicin/Olaratumab (increase OS)
	Doxil (Liposomal Doxorubicin)
	Gemcitibine/Docetaxel
	Pazopanib (TKI)
	Ifosfamide
	Dacarbazine
	Clinical Trials

<u>High Grade UPS</u>

Neoadjuvant/adjuvant

First Line	AIM (Adriamycin (doxorubicin)/Ifosfamide/Mesna)

Leimyosarcoma (LMS)

Leimyosarcoma is a rare malignant spindle cell tumor (sarcoma) composed of cells, which demonstrate smooth muscle differentiation. Almost 50% percent affect the retroperitoneum.

Leiomyosarcoma have been subdivided into 3 categories:

1. leiomyosarcoma of peritoneum
2. leiomyosarcoma of deep soft tissues outside the peritoneum
3. leiomyosarcoma of subcutaneous tissues.

Prognosis depends on grade, size and location of the tumor.

Clinical Data

Affect age group of 40 to 60 years.
Represents almost 9% of all soft tissue sarcomas
Present often as a painless mass

Sites
Retroperitoneum (first place with almost 50%)
Thigh (second most common area)
Subcutaneous distribution (6%)
Can arise from the wall of the blood vessel (location of smooth muscle)

Signs/Symptoms
Slow-growing mass
Soft tissue mass that may be or not be painful, and tender (retroperitoneum)
Usually do not develop symptoms until the mass grows more than 10 cm (retroperitoneum)
Almost all tumors outside of the peritoneum are painless

Prevalence
Preference for women
Except subcutaneuous tissue, preference for male.
Third most common soft tissue sarcoma.
Mostly middle-aged and older adults
Small subset of children (immunosuppressed, HIV)--->deep soft tissue other than retroperitoneum

Site
Almost 50% of the cases located in retroperitoneal area
Extremities, particularly lower/thigh area

Radiographic Presentation

Plain x-ray
No specific radiological features (demonstrate soft tissue mass)
Calcifications are rare

CT

Frequently demonstrate areas of low attenuation,--->heterogeneous areas (hemorrhage, necrosis, or cystic change)

Immunohistochemstry

Desmin and Actin are positive (Fig. 9,10 - above)
Vimentin Positive
Keratin negative

Prognosis

Biological Behavior
Tumors located in an extremity have 50% survival at 5 years.
Retroperitoneal tumors have 25-35% 5 year survival
Earlier diagnosis with deep soft tissue masses and subcutaneous tumors compared to retroperitoneal tumors
More easily noticeable
Less aggressive
Smaller size
Usually a prolonged period of time for diagnosis in retroperitoneoum
Retroperitoneal lesions: 25-35% survival at 5 years.
Extremely aggressive
Invade neighboring organs
Grow more than 10 cm in Ø more than 1,500 gr

Often metastasize to:
Lung
Liver
Bone
Other soft tissues
Lymph nodes

Treatment

If is possible, wide resection and postoperative radiation whenever feasible chemotherapy and/ or radiotherapy can be implemented

Chemotherapy Regimes:

First Line	Gemcitibine/Docetaxel
Second Line	Doxorubicin/Olaratumab
Third Line	Trabectedin
	Pazopanib (Votrient) -TKI
	Dacarbazine

Synovial Sarcoma

Synovial sarcoma is a common soft tissue malignancy accounting for 5 – 10 % of soft tissue sarcomas. Patients with synovial cell sarcoma are often between the ages of 15 and 35 years old; generally younger than patients with other types of soft tissue sarcomas.

The most probable cellular origin is an undifferentiated mesenchymal cell.

The tumor may be monophasic or biphasic meaning having one or two different types of cells that make up the tumor. The monophasic type is frequently composed of relatively uniform malignant appearing spindle cells with a fascicular arrangement. The biphasic type is similar to the monophasic but with epithelial clusters or glandular-like spaces.
Synovial sarcoma has a fusion gene, SYT-SSX, which is the result of a chromosomal translocation unique for this tumor, t(x;18)(p11;q11), which is present in up to 90% of cases. Synovial sarcoma whether monophasic or biphasic stains positive for vimentin and epithelial makers such as cytokeratin and epithelial membrane antigen (EMA)

Clinical Data

Third most common soft tissue sarcoma; 6-10%
Most commonly affects young adults aged between 15 and 35 years
Equal male and female prevalence
Occurs most often in paraarticular regions and not in the actual joints.
It can arise from tendon sheaths, bursae or joints capsules.
Most common soft tissue sarcoma of the foot and ankle

Signs/Symptoms
Slow growing, palpable and often painful mass.
Symptoms may be present from days to as long as 20 years before initial diagnosis

Prevalence
Equal prevalence male and female

Age
Range 15 - 35 years old
Generally presents in a younger age than other soft tissue sarcomas

Sites
Most synovial sarcomas occur in the extremities (80%).
Predilection for lower limbs 60 – 70 %
Popliteal fossa being the most common location.
Most common soft tissue malignancy of the foot and ankle in patients between 6 and 35 years old.
Most of them are intermuscular in location and found within 5 cm of a joint.
Intra-articular origin is found in less than 10 % of the cases.
It can invade adjacent bone
May metastasize to regional lymph nodes

Radiographic Presentation

X-rays
Normal in approximately 50% of the cases.
Soft tissue density with mineralization in 30% of cases. This type of mineralization usually presents as calcifications with an irregular contour often in a peripheral distribution.
In 11% to 20% of cases there may be a periosteal reaction, adjacent bony erosion or bone invasion.

Gross Pathology
Synovial sarcomas are usually circumscribed, round or multilobular masses
They may grow to >15 cm, but on average measure 3 to 5 cm in greatest diameter since many occur in the foot and ankle
Can be described as yellow to gray-white
The less differentiated variants often grow more rapidly and tend to be poorly circumscribed, with multiple areas of hemorrhage, necrosis, and cystic formation

Microscopic Pathology
Synovial Sarcoma is composed of two different cell types:
-Spindle cell (small, uniform, and ovoid cells with pale nuclei and the cytoplasm is sparse)
-Epitheloid cell (ovoid nuclei and abundant cytoplasm)
Biphasic form is composed of both epithelial-cell and spindle-cell components in equal proportions
Monophasic Fibrous type predominantly spindle cell.
Monophasic Epithelial type is difficult to differentiate from adenocarcinoma without cytogenetics and immunohistochemistry.
Poorly differentiated type demonstrates features of high grade small round cell tumor with dense cellularity, numerous mitotic figures, and areas of necrosis.
Inmunohistochemical profile: Vimentin (+), Cytokeratin (+), Epithelial Membrane Antigen EMA (+)

Treatment

Wide surgical excision is the mainstay of treatment for Synovial Sarcoma
High grade tumors:
Often requires either radical resection or wide surgical excision plus Radiotherapy

Amputation may be required for unresectable tumors
Tumors that are greater than 8 cm in diameter may be considered for administering Chemotherapy and Radiotherapy
Radiotherapy may improve local control
Chemotherapy is most often used when there is metastatic disease

Prognosis

5-year survival rates vary significantly, ranging from 36 to 76%
Large tumor size (> 5 cms), presence of bone or neurovascular invasion were found to be associated with the development of distant metastasis and decreased disease specific survival (mortality).
Patients with tumors that present with more than 20% of poorly differentiated patterns have the worse prognosis.

50% of the patients with Synovial Sarcoma develop metastases.
Other prognostic factors have been correlated with an increase in the local recurrence rate including; proximal location of the tumor or positive margin after resection.

Chemotherapy Regimes:

First Line	AIM (Adriamycin (doxorubicin)/Ifosfamide/Mesna)
	Doxorubicin/Olaratumab
Second Line	Cyclophophamide and NY-ESO T cells (Clinical Trial?)
	Pazopanib (Votrient) -TKI
	Doxorubicin/Olaratumab
	Clinical Trials

Extraskeletal Ewing Sarcoma (EES)

Extraskeletal Ewing Sarcoma (EES) is a malignant small round-blue cell tumor than arises most often in Children and adolescents. Tefft et al in 1969 described the first series of Extraskeletal Ewing Sarcoma that arose from the paravertebral soft tissues. Ewing sarcoma, although a rare type of sarcoma, is most typically a type of sarcoma that arises from bone. However more rarely Ewing Sarcoma can arise from the soft tissues and is then termed Extraskeletal Ewing Sarcoma. EES is a rare tumor composed of monotonous primitive small round blue-celsl distributed in pieces or lobules. It's has an annual incidence rate of 1-3 cases per million. Ewing sarcoma and primitive neuroectodermal (PNET) tumor fall in the same family of tumors.

Clinical Data

High grade sarcoma
• Rare soft tissue tumor, indistinguishable from

Ewing sarcoma of bone
• Usually affects patients age 30 or less, occasionally age >50
• Slight male preference
• Most commonly metastasizes to lung and bones

Sign/Symptoms
• Usually a large and deep mass
• Rarely subcutaneous
• Rapidly growing
• Usually painless (pain in 30% of cases)

Prevalence
• Much less common than skeletal Ewing sarcoma
• Slight predilection for males
• Rarely effects Afro-Americans
• Occurs in all ages but usually younger population
• Preference for individuals between 15 and 40 years

Site
• Commonly in soft tissue of lower extremities and thorax

Radiographic presentation

Plain x-ray
• No specific radiological features
• May reveal a soft tissue mass
• No mineralization
• If adjacent to a bone may show underlying bony erosion

CT
• Shows attenuation similar to the muscle
• May be heterogenous with areas of necrosis and hemorrhage

MRI

• Low to intermediate signal intensity on T1W
• High signal intensity on T2W
• Usually heterogeneous from necrosis and hemorrhage

Immunohistochemistry

Positive
o CD 99
o PSA
o Vimentin
• Negative
o S-100
o NF
o CK 7
o CK 19
o Leukocyte antigen

Prognosis

Biological Behavior
Tumor cells often express MIC2 gene
o Demonstrate several novel reciprocal chromosomal translocations and fusion gene transcripts
o t(11;22) chromosomal translocation most commonly encountered and often aides in diagnosis

• High rate of metastasis
o Most commonly in the lungs and bones
• Best prognosis in patients age<16 years who underwent surgical resection and chemotherapy.
• Patients with metastatic disease generally die within 2 years
• 50% 5-years survival rate in patients who present with localized disease

Treatment

Complete excision; Limb Sparing Surgery
• Radiotherapy may be indicated
• Multi-drug chemotherapy (cyclophospphamide, ifosfamide, etoposide, doxorubicin and vincristine)

Classic Kaposi Sarcoma

First Line Doxil (liposomal Doxorubicin)

Second line pomalidomide (recently approved)

Positive for HHV8

Check HIV AB, HIV PCR

Avoid all steroids

GASTROINTESTINAL STROMAL TUMORS (GISTs)

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal tract. GISTs arise in the smooth muscle pacemaker interstitial cell of Cajal, or similar cells. They are defined as tumors whose behavior is driven by mutations in the KIT gene (85%),PDGFRA gene (10%), or BRAF kinase (rare). 95% of GISTs stain positively for KIT (CD117). Most (66%) occur in the stomach and gastric GISTs have a lower malignant potential than tumors found elsewhere in the GI tract.

GIST was introduced as a diagnostic term in 1983. Until the late 1990s, many non- epithelial tumors of the gastrointestinal tract were called "gastrointestinal stromal tumors". Histopathologists were unable to specifically distinguish between types we now know to be dissimilar molecularly. Subsequently, CD34, and later CD117 were identified as markers that could distinguish the various types. Additionally, in the absence of specific therapy, the diagnostic categorization had only a limited influence on prognosis and therapy.

The understanding of GIST biology changed significantly with identification of the molecular basis of GIST, particularly c-KIT. Historically, literature reviews prior to the molecular definition of GIST, and for a short time thereafter, asserted that 70-80% of GISTs were benign. The identification of a molecular basis for GIST led to the exclusion of many tumors that had been considered as GIST previously, and also the incorporation of a much larger number of tumors that had been labeled as other types of sarcomas and undifferentiated carcinomas. For example, some previous diagnoses of stomach and small bowel leiomyosarcomas (malignant tumor of smooth muscle) would be reclassified as GISTs on the basis of immunohistochemical staining. All GIST tumors are now considered to have malignant potential, and no GIST tumor can be definitively classified as "benign". Hence, all GISTs are eligible for cancer staging in the AJCC (7th edition) / UICC. Nonetheless, different GISTs have different risk assessments of their tendency to recur or to metastasize, dependent on their site of origin, size, and number of mitotic figures.

Due to the change in definition, clinical pathways of care before the year 2000 are largely uninformative in the current era.

Sign/Symptoms
GISTs may present with trouble swallowing, gastrointestinal bleeding, or metastases (mainly in the liver). Intestinal obstruction is rare, due to the tumor's outward pattern of growth. Often, there is a history of vague abdominal pain or discomfort, and the tumor has become rather large by time the diagnosis is made.

Pathophysiology
GISTs are tumors of connective tissue, i.e. sarcomas; unlike most gastrointestinal tumors, they are nonepithelial. About 70% occur in the stomach, 20% in the small intestine and less than 10% in the esophagus. Small tumors are generally benign, especially when cell division rate is slow, but large

tumors disseminate to the liver, omentum, and peritoneal cavity. They rarely occur in other abdominal organs.

GISTs are thought to arise from interstitial cells of Cajal (ICC), that are normally part of the autonomic nervous system of the intestine. They serve a pacemaker function in controlling motility.

Genetics
Most GISTs are sporadic. Less than 5% occur as part of hereditary familial or idiopathic multitumor syndromes. These include, in descending order of frequency, neurofibromatosis Recklinghausen (NF-1), Carney's triad (gastric GIST, pulmonary chondroma and (extra- adrenal paraganglioma), germline gain-of-function mutations in a c-Kit/PDGFRA, and the Carney-Stratakis syndrome.[8] The Carney-Stratakis syndrome is a dyad of hereditary GIST and paraganglioma, that is caused by germline mutations in the mitochondrial tumor suppressor gene pathway involving the succinate dehydrogenase (SDH) subunits SDHD, SDHC, and SDHB. Carney's triad does not feature SDH mutations.

c-KIT mutations
Approximately 85% GISTs are associated with an abnormal *c-kit* pathway. *c-KIT* is a gene that encodes for a transmembrane receptor for a growth factor termed stem cell factor (*scf*). The abnormal *c-KIT* pathway most commonly (85%) arises from mutation of the gene itself; a smaller subset of c-KIT-associated GISTs are associated with constitutive activity of the *KIT* enzymatic pathway, found by immunoblotting. The c-KIT product/CD117 is expressed on ICCs and a large number of other cells, mainly bone marrow cells, mast cells, melanocytes and several others. In the gut, however, a mass staining positive for CD117 is likely to be a GIST, arising from ICC cells.
The c-KIT molecule comprises a long extracellular domain, a transmembrane segment, and an intracellular part. Mutations generally occur in the DNA encoding the intracellular part (exon 11), which acts as a tyrosine kinase to activate other enzymes. Mutations make c-KITfunction independent of activation by *scf*, leading to a high cell division rate and possibly genomic instability. Additional mutations are likely "required" for a cell with a *c-KIT* mutation to develop into a GIST, but the *c-KIT*mutation is probably the first step of this process.
Mutations in the exons 11, 9 and rarely 13 and 17 of the *c-KIT* gene are known to occur in GIST. The tyrosine kinase function of *c-KIT* is important in the medical therapy for GISTs, as described below.

- KIT-D816V point mutations in *c-KIT* exon 17 are responsible for resistance to targeted therapy drugs like imimatinib mesylate, a tyrosine kinase inhibitor.
- KIT-p.D419del (exon 8) - A subset of gastrointestinal stromal tumors previously regarded as wild-type tumors carries somatic activating mutations in KIT exon 8 (p.D419del).

PDGFRA mutations
Most GIST cells with wildtype (i.e. not mutated) *c-kit* instead have a mutation in another gene, PDGFR-α (platelet derived growth factor receptor alpha), which is a related tyrosine kinase. Mutations in *c-kit* and *PDGFrA* are mutually exclusive.

Wild-type tumors
Lesser numbers of GISTs appear to be associated with neither c-kit nor PDGFR-α abnormalities. About 10-15% of gastrointestinal stromal tumors (GISTs) carry wild-type sequences in all hot spots of KIT and platelet-derived growth factor receptor alpha (PDGFRA) (wt-GISTs). These tumors are currently defined by having no mutations in exons 9, 11, 13, and 17 of the KIT gene and exons 12, 14, and 18 of the PDGFRA gene.

Diagnosis
CT Scanning is often undertaken.
The definitive diagnosis is made with a biopsy, which can be obtained endoscopically, percutaneously with CT or ultrasound guidance or at the time of surgery. A biopsy sample will be investigated under the microscope by a pathologist physician. The pathologist examines the histopathology to identify the characteristics of GISTs (spindle cells in 70-80%, epitheloid aspect in 20-30%). Smaller tumors can usually be confined to the muscularis propria layer of the intestinal wall. Large ones grow, mainly outward, from the bowel wall until the point where they outstrip their blood supply and necrose (die) on the inside, forming a cavity that may eventually come to communicate with the bowel lumen.
When GIST is suspected—as opposed to other causes for similar tumors—the pathologist can use immunohistochemistry (specific antibodies that stain the molecule CD117 [also known as *c-kit*] —see below). 95% of all GISTs are CD117-positive (other possible markers include CD34, DOG-1, desmin, and vimentin). Other cells that show CD117 positivity are mast cells.

If the CD117 stain is negative and suspicion remains that the tumor is a GIST, the newer antibody DOG-1 (Discovered on GIST-1) can be used. Also sequencing of Kit and PDGFRA can be used to prove the diagnosis.

Imaging

The purpose of radiologic imaging is to locate the lesion, evaluate for signs of invasion and detect metastasis. Features of GIST vary depending on tumor size and organ of origin. The diameter can range from a few millimeters to more than 30 cm. Larger tumors usually cause symptoms in contrast to those found incidentally which tend to be smaller and have better prognosis. Large tumors tend to exhibit malignant behavior but small GISTs may also demonstrate clinically aggressive behavior.

Small GISTs

Since GISTs arise from the bowel layer called muscularis propria (which is deeper to the mucosa and submucosa from a luminal perspective), small GIST imaging usually suggest a submucosal process or a mass within the bowel wall. In barium swallow studies, these GISTs most commonly present with smooth borders forming right or obtuse angles with the nearby bowel wall, as seen with any other intramural mass. The mucosal surface is usually intact except for areas of ulceration, which are generally present in 50% of GISTs. Ulcerations fill with barium causing a bull's eye or target lesion appearance. In contrast-enhanced CT, small GISTs are seen as smooth, sharply defined intramural masses with homogeneous attenuation.

Large GISTs

As the tumor grows it may project outside the bowel (exophytic growth) and/or inside the bowel (intraluminal growth), but they most commonly grow exophytically such that the bulk of the tumor projects into the abdominal cavity. If the tumor outstrips its blood supply, it can necrose internally, creating a central fluid-filled cavity with bleeding and cavitations that can eventually ulcerate and communicate into the lumen of the bowel. In that case, barium swallow may show an air, air-fluid levels or oral contrast media accumulation within these areas. Mucosal ulcerations may also be present. In contrast enhanced CT images, large GISTs appear as heterogeneous masses due to areas of living tumor cells surrounding bleeding, necrosis or cysts, which is radiographically seen as a peripheral enhancement pattern with a low attenuation center. In MRI studies, the degree of necrosis and bleeding affects the signal intensity pattern. Areas of bleeding within the tumor will vary its signal intensity depending on how long ago the bleeding occurred. The solid portions of the tumor are typically low signal intensity on T1-weighted images, are high signal intensity on T2 weighted images and enhance after administration of gadolinium. Signal-intensity voids are present if there is gas within areas of necrotic tumor.

Features of malignancy

Malignancy is characterized by local invasion and metastases, usually to the liver, omentum, and peritoneum. However, cases of metastases to bone, pleura, lungs and retroperitoneum have been seen. In distinction to gastric adenocarcinoma or gastric/small bowel lymphoma, malignant lymphadenopathy (swollen lymph nodes) is uncommon (<10%) and thus imaging usually shows absence of lymph node enlargement. If metastases are not present, other radiologic features suggesting malignancy include: size (>5 cm), heterogeneous enhancement after contrast administration and ulcerations. Also, overtly malignant behavior (in distinction to malignant potential of lesser degree) is less commonly seen in gastric tumors, with a ratio of behaviorally benign to overtly malignant of 3-5:1.[3] Even if radiographic malignant features are present, these findings may also represent other tumors and definitive diagnosis must be made immunochemically.

Management
In localized, resectable adult GISTs, if anatomically and physiologically feasible, surgery is the primary treatment of choice. Surgery can be potentially curative, but watchful waiting may be considered in small tumors in carefully selected situations. Post-surgical adjuvant treatment may be recommended. Lymph node metastases are rare, and routine removal of lymph nodes is typically not necessary. Laparoscopic surgery, a minimally invasive abdominal surgery using telescopes and specialized instruments, has been shown to be effective for removal of these tumors without needing large incisions. The clinical issues of exact surgical indications for tumor size are controversial. The decision of appropriate laparoscopic surgery is affected by tumor size, location, and growth pattern.
Radiotherapy has not historically been effective for GISTs and GISTs do not respond to most chemotherapy medications, with responses in less than 5%. However, three medications have been identified for clinical benefit in GIST: imatinib, sunitinib, and regorafenib.

Imatinib (Glivec/Gleevec), an orally administered drug initially marketed for chronic myelogenous leukemia based on bcr-abl inhibition, also inhibits both *c-kit tyrosine* mutations and PDGFRA mutations other than D842V, is useful in treating GISTs in several situations. Imatinib has been used in selected neoadjuvant settings. In the adjuvant treatment setting, the majority of GIST tumors are cured by surgery, and do not need adjuvant therapy. However, a substantial proportion of GIST tumors have a high risk of recurrence as estimated by a number of validated risk stratification schemes, and can be considered for adjuvant therapy. The selection criteria underpinning the decision for possible use of imatinib in these settings include a risk assessment based on pathological factors such as tumor size, mitotic rate, and location can be used to predict the risk of recurrence in GIST patients. Tumors <2 cm with a mitotic rate of <5/50 HPF have been shown to have lower risk of recurrence than larger or more aggressive tumors. Following surgical resection of GISTs, adjuvant treatment with imatinib reduces the risk of disease recurrence in higher risk groupsIn selected higher risk adjuvant situations, imatinib is recommended for 3 years.

Imatinib was approved for metastatic and unresectable GIST by the US FDA, February 1, 2002. The two-year survival of patients with advanced disease has risen to 75–80% following imatinib treatment.
If resistance to imatinib is encountered, the multiple tyrosine kinase inhibitor sunitinib (marketed as Sutent) can be considered.

The effectiveness of imatinib and sunitinib depend on the genotype. cKIT- and PDGFRA-mutation negative GIST tumors are usually resistant to treatment with imatinib[9] as is neurofibromatosis-1-associated wild-type GIST. A specific subtype of PDGFRA-mutation, D842V, is also insensitive to imatinib.
Regorafenib (Stivarga) was FDA approved in 2013 for advanced GISTs that cannot be surgically removed and that no longer respond to imatinib (Gleevec) and sunitinib (Sutent).

Epidemiology
GISTs occur in 10-20 per one million people. The true incidence might be higher, as novel laboratory methods are much more sensitive in diagnosing GISTs.The estimated incidence of GIST in the United States is approximately 5000 cases annually. This makes GIST the most common form of sarcoma, which constitutes more than 70 types of cancer.

The majority of GISTs present at ages 50–70 years. Across most of the age spectrum, the incidence of GIST is similar in men and women.

Adult GISTs are rare before age 40. Pediatric GISTs are considered to be biologically distinct. Unlike GISTs at other ages, pediatric GISTs are more common in girls and young women. They appear to lack oncogenic activating tyrosine kinase mutations in both KIT and PDGFRA. Pediatric GISTs are treated differently than adult GIST. Although the generally accepted definition of pediatric GIST is a tumor that is diagnosed at the age of 18 years or younger, "pediatric-type" GISTs can be seen in adults, which affects risk assessment, the role of lymph node resection, and choice of therapy.

Tx- Surgery followed by targeted oral agents.

Neoadjuvant Imatinib helpful to decrease tumor size

Adjuvant to prevent recurrence (>5cm, non-gastric, high mitotic)

Molecular testing needed (Impac) KIT (80%), PDGFR 10%)

- Imatinib (Gleevac) 400mg daily
- Sunitinib 37.5 mg daily
- Regorafenib 160mg daily x 21 day, off 7 days
- Pazopanib, nilotinib, sorafenib

Ewing's sarcoma

Ewing's sarcoma is a malignant small, round, blue cell tumor malignant small round blue cell tumor. It is a rare disease in which cancer cells are found in the bone or in soft tissue. The most common areas in which it occurs are the pelvis, the femur, the humerus, the ribs and clavicle.
Since a common genetic locus is responsible for a large percentage of Ewing's sarcoma and primitive neuroectodermal tumors, these are sometimes grouped together in a category known as the Ewing family of tumors.
Ewing's sarcoma occurs most frequently in teenagers and young adults, with a male/female ratio of 1.6:1.
Although usually classified as a bone tumour, Ewing's sarcoma can have characteristics of both mesodermal and ectodermal origin, making it difficult to classify.
James Ewing (1866–1943) first described the tumour, establishing that the disease was separate from lymphoma and other types of cancer known at that time.

Causes
Genetic exchange between chromosomes can cause cells to become cancerous. Most cases of Ewing's sarcoma (85%) are the result of a translocation between chromosomes 11 and 22, which fuses the EWS gene of chromosome 22 to the FLI1 gene of chromosome 11.
EWS/FLI functions as the master regulator.
Other translocations are at t(21;22) and t(7;22).
Ewing's sarcoma cells are positive for CD99 and MIC2, and negative for CD45

Clinical Findings

Distribution of Ewing's sarcoma: most frequent locations are the large long bones and the pelvis
Ewing's sarcoma is more common in males (1.6 male:1 female) and usually presents in childhood or early adulthood, with a peak between 10 and 20 years of age. It can occur anywhere in the body, but most commonly in the pelvis and proximal long tubular bones, especially around the growth plates. The diaphyses of the femur are the most common sites, followed by the tibia and the humerus. Thirty percent are overtly metastatic at presentation. Patients usually experience extreme bone pain.
Signs and symptoms include: intermittent fevers, anemia, leukocytosis, increased sedimation rate, and other symptoms of inflammatory systemic illness.[6] Also, depending on the type, progression, and location of the tumor - great pain may occur.
According to the Bone Cancer Research Trust (BCRT), the most common symptoms are: localized pain, swelling, and sporadic bone pain with variable intensity. The swelling is most likely to be visible if the sarcoma is located on a bone near the surface of the body, but when it occurs in other places deeper in the body, like on the pelvis, it may not be visible

Imaging

MRI should be routinely used in the work-up of malignant tumors. It will show the full bony and soft tissue extent and relate the tumor to other nearby anatomic structures (e.g. vessels). Gadolinium contrast is not necessary as it does not give additional information over noncontrast studies, though some current researchers argue that dynamic, contrast-enhanced MRI may help determine the amount of necrosis within the tumor, thus help in determining response to treatment prior to surgery.
CT can also be used to define the extraosseous extent of the tumor, especially in the skull, spine, ribs, and pelvis. Both CT and MRI can be used to follow response to radiation and/or chemotherapy. Bone scintigraphy can also be used to follow tumor response to therapy.
In the group of malignant small round cell tumors which include Ewing's sarcoma, bone lymphoma, and small cell osteosarcoma, the cortex may appear almost normal radiographically, while permeative growth occurs throughout the Haversian channels. These tumours may be accompanied by a large soft-tissue mass while almost no bone destruction is visible. The radiographs frequently do not shown any signs of cortical destruction.
Radiographically, Ewing's sarcoma presents as "moth-eaten" destructive radiolucencies of the medulla and erosion of the cortex with expansion.

Diagnosis
The definitive diagnosis is based on histomorphic findings, immunohistochemistry and molecular pathology.
Ewing's sarcoma is a small –blue-round-cell tumor that typically has a clear cytoplasm on H&E staining, due to glycogen. The presence of the glycogen can be demonstrated with positive PAS staining and negative PAS diastase staining. The characteristic immunostain is CD99, which diffusely marks the cell membrane. Morphologic and immunohistochemical findings are corroborated with an associated chromosomal translocation, of which several occur. The most common translocation, present in about 90% of Ewing sarcoma cases, is t(11;22)(q24;q12), which generates an aberrant transcription factor through fusion of the *EWSR1* gene with the *FLI1* gene.
The pathologic differential diagnosis is the grouping of small-blue-round-cell tumors, which includes lymphoma, alveolar rhabdomyosarcoma, and desmoplastic small round cell tumor, among others.

Epidemiology
Ewing's sarcomas represent 16% of primary bone sarcomas. In the United States, they are most common in the second decade of life, with a rate of 0.3 cases per million in children under 3 years of age, and as high as 4.6 cases per million in adolescents aged 15–19 years. Internationally, the annual incidence rate averages less than 2 cases per million children. In the United Kingdom, an average of six children per year are diagnosed, mainly males in early stages of puberty. Due to the prevalence of diagnosis during teenage years, a link may exist between the onset of puberty and the early stages of this disease, although no research confirms this hypothesis.
The oldest known patient diagnosed was at age 76, from the Mercer County, NJ, area.
A grouping of three unrelated teenagers in Wake Forest, NC, have been diagnosed with Ewing's sarcoma. All three children were diagnosed in 2011 and all attended the same temporary classroom together while the school underwent renovation. A fourth teenager living nearby was diagnosed in 2009. The odds of this grouping are considered significant.
Ewing's sarcoma shows striking differences in incidence across human populations and is about 10- to 20-fold more common in populations from European descent as compared to Africans. Consistently, a genome-wide association study (GWAS) conducted in several hundreds European individuals with Ewing's sarcoma and genetically-matched healthy controls identified three susceptibility loci located on chromosomes 1, 10 and 15. A continuative study discovered that the Ewing's sarcoma susceptibility gene EGR2, which is located within the chromosome 10 susceptibility locus, is regulated by the *EWSR1-FLI1* fusion oncogene via a GGAA-microsatellite.

Ewing sarcoma is the second most common bone cancer in children and adolescents, with poor prognosis and outcome in ~70% of initial diagnoses and 10–15% of relapses.

Treatment
Almost all patients require multidrug chemotherapy (often including ifosfamide and etoposide), as well as local disease control with surgery and/or radiation. An aggressive approach is necessary because almost all patients with apparently localized disease at the time of diagnosis actually have asymptomatic metastatic disease.
Treatment often consists of neoagjuvant chemotherapy, which may include vincristine, doxorubicin, and cyclophosphamide, with ifosfamide and etoposide. After about three months of chemotherapy, the

remaining tumor is surgically resected, irradiated, or both. The surgical resection may involve limb salvage or amputation. Complete excision at the time of biopsy may be performed if malignancy is confirmed at the time it is examined.
Treatment lengths vary depending on location and stage of the disease at diagnosis. Radical chemotherapy may be as short as six treatments at 3-week cycles, but most patients undergo chemotherapy for 6–12 months and radiation therapy for 5–8 weeks. Radiotherapy has been used for localized disease. The tumor has a unique property of being highly sensitive to radiation, sometimes acknowledged by the phrase "melting like snow", but the main drawback is that it recurs dramatically after some time. Antisense oligodeoxynucleotides have been proposed as possible treatment by down-regulating the expression of the oncogenic fusion protein associated with the development of Ewing's sarcoma resulting from the EWS-ETS gene translocation. In addition, the synthetic retinoid derivative fenretinide (4-hydroxy(phenyl)retinamide) has been reported to induce high levels of cell death in Ewing's sarcoma cell lines *in vitro* and to delay growth of xenografts in *in vivo* mouse models.

Fertility preservation
In women, chemotherapy may damage the ovaries and cause infertility. To avail future pregnancies, the woman may preserve oocytes or ovarian tissue by oocyte cryopreservation or ovarian tissue cryopreservation prior to starting chemotherapy. However, the latter may reseed the cancer upon reinsertion of the ovarian tissue. If it is performed, the ovarian tissue should be examined for traces of malignancy at both the pathological and molecular levels prior to the grafting of the cryopreserved tissue.

Prognosis
Staging attempts to distinguish patients with localized from those with metastatic disease. Most commonly, metastases occur in the chest, bone and/or bone marrow. Less common sites include the central nervous system and lymph nodes.
Five-year survival for localized disease is 70% to 80% when treated with chemotherapy. Prior to the use of multi-drug chemotherapy, long-term survival was less than 10%. The development of multi-disciplinary therapy with chemotherapy, irradiation, and surgery has increased current long-term survival rates in most clinical centers to greater than 50%. However, some sources state it is 25–30%.
Retrospective research in patients led by Idriss M. Bennani-Baiti (Cancer Epigenetics Society) showed that two chemokine receptors, CXCR4 and CXCR7, can be used as molecular prognosis factors. Patients who express low levels of both chemokine receptors have the highest odds of long-term survival with >90% survival at 5 years post-diagnosis versus <30% survival at 5 years for patients with very high expression levels of both receptors.

Chemotherapy regimens:
Molecular Genetics

IMPAC – Secondary germline

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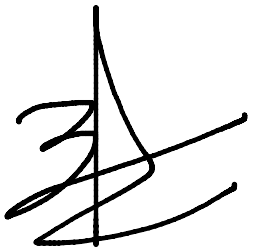
Firma 

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