**DEFINITION**

- Soft tissue pathology deals with tumors of the connective tissues.
- The concept of soft tissue is understood broadly to include non-osseous tumors of extremities, trunk wall, retroperitoneum and mediastinum, and head & neck.
- Excluded (with a few exceptions) are organ specific tumors.

**CLASSIFICATION**

- Purpose of classification is to link similar tumors in order to understand their behavior, determine the most appropriate treatment, and investigate their biology.
- However, purpose of a classification system is simplicity and reproducibility.
- Therefore tumors are classified according to the cell type they resemble.
- Refinements are coming from cytogenetics, molecular, and gene expression studies.
- The majority arise from -or show differentiation toward- mesenchymal cells, but some show other differentiation (neuroectodermal, histiocytic).
- A small subset is of unknown histogenesis.

**DEFINITION**

- Bone pathology deals with tumors of the skeletal system.
- Included are subsets of tumors from extra-osseous sites that show osseous and cartilaginous differentiation.

**CLASSIFICATION**

- Many tumors resemble tissues present in the region of origin.
- These tumors may be derived from stem cells that belong to local, organ-specific pools.
- Other involved stem cells may be bone marrow derived.
- Some tumors have no resemblance to normal tissue in the region (metaplastic foci within a tumor, or tumors of different histogenesis from the normal cells of the region).
- Some sarcomas have no normal cell counterparts, probably reflecting an unique genetic makeup.
CLASSIFICATION

- Tumors are also classified according to their biologic potential.
- A three-tiered system is used:
  - 1. Benign
  - 2. Borderline (intermediate malignant)

EPIDEMIOLOGY

- The knowledge of epidemiologic data may help in diagnosis.

EPIDEMIOLOGY

- Soft tissue (ST) sarcomas are rare tumors compared to other malignancies: 8,700 new sarcomas in 2001, with 4,400 deaths.
- The incidence of ST sarcomas in the USA is approximately 3.3 cases per 100,000 people.
- This is roughly 5% of each of some of the most common carcinomas (prostate, breast, lung), half of all brain tumors, and approximately equal to AML.

EPIDEMIOLOGY

- There is a slight male predominance (with some subtypes more common in women).
- The majority of soft tissue tumors affect older adults (some subgroups occur predominantly or exclusively in children).
- Incidence of benign soft tissue tumors not known, but probably outnumber malignant tumors 100:1.

BONE TUMORS - EPIDEMIOLOGY

- Primary bone tumors are rare.
- Bone sarcomas account for 0.2% of all neoplasms (SEER Cancer Statistics Review, 1973-1996).
- Soft tissue sarcomas are approximately 10 times more common than primary bone sarcomas.
BONE TUMORS - EPIDEMIOLOGY

- The majority of tumors involving bone are secondary (or metastatic):
  - secondary (metastases) (95%)
  - primary (5%)

---

ETIOLOGY

- The etiology of sarcomas is poorly understood, and what is known apply only to a small fraction of the group.
- The known etiologic agents are ionizing radiation, oncogenic viruses, and chemicals.
- These agents are able to cause genetic alterations that can lead to tumorigenesis.

---

Secondary Tumors of Bone

- The carcinomas most frequently involved with bone metastasis originate from:
  - Lung
  - Breast
  - Prostate
  - G.I
  - Kidney
  - Thyroid

---

BONE TUMORS

- Bone sarcomas as a group have a bimodal distribution.
- The first peak is in the second decade.
- The second peak occurs in patients older than sixty.
ETIOLOGY

- Herbicides ("agent orange") and peripheral soft tissue sarcomas
- Retained metal objects (shrapnel, surgical devices) and OS, AS and MFH
- Vinyl chloride, inorganic arsenic, Thorotrast, anabolic steroids linked to AS and MFH.

Host factors may also play a role in the development of soft tissue sarcomas.

- Immunosuppression, besides Kaposi’s sarcoma, may be associated with sarcomas.
- Lymphedema, congenital or acquired (post-mastectomy) is a rare cause of extremity-based AS.

CONGENITAL SYNDROMES ASSOCIATED WITH BONE AND SOFT TISSUE TUMORS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Locus</th>
<th>Gene</th>
<th>Tumor</th>
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</thead>
<tbody>
<tr>
<td>Albright hereditary osteodystrophy</td>
<td>AD</td>
<td>20q13</td>
<td>GNAS1</td>
<td>Soft tissue calcifications and osteomas</td>
</tr>
<tr>
<td>Bannayan-Riley-Ruvalcaba syndrome</td>
<td>AD</td>
<td>10q23</td>
<td>PTEN</td>
<td>Lipomas, hemangiomas</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome</td>
<td>Sp/AD</td>
<td>11p15</td>
<td>Complex</td>
<td>Embryonal RMS, myxomas, fibromas, hamartomas</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>AR</td>
<td>15q26</td>
<td>BLM</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Carney complex (Familial myxoma syndrome)</td>
<td>AD</td>
<td>17q23-24</td>
<td>2p16</td>
<td>PRKAR1AK</td>
</tr>
<tr>
<td>Costello syndrome</td>
<td>Sporadic</td>
<td>-</td>
<td>-</td>
<td>Rhabdomyosarcomas</td>
</tr>
<tr>
<td>Cowden disease (Multiple hamartoma syndrome)</td>
<td>AD</td>
<td>10q23</td>
<td>PTEN</td>
<td>Lipomas, Hemangiomas</td>
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<tr>
<td>Diaphyseal medullary stenosis</td>
<td>AD</td>
<td>9p21-22</td>
<td>-</td>
<td>MFH</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>AD</td>
<td>5q21</td>
<td>APC</td>
<td>Craniofacial osteomas, desmoid tumors</td>
</tr>
<tr>
<td>Familial expansile osteolysis</td>
<td>AD</td>
<td>18q21</td>
<td>TNFRSF11A</td>
<td>Osteosarcomas</td>
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<tr>
<td>Familial infiltrative fibromatosis</td>
<td>AD</td>
<td>5q21</td>
<td>APC</td>
<td>Desmoid tumors</td>
</tr>
<tr>
<td>Langer-Giedion syndrome</td>
<td>Sporadic</td>
<td>8q24</td>
<td>EXT1</td>
<td>Osteochondromas, chondrosarcomas</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>AD</td>
<td>17p13</td>
<td>TP53</td>
<td>CHEK2</td>
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<tr>
<td>Maffucci syndrome</td>
<td>Sporadic</td>
<td>-</td>
<td>-</td>
<td>Enchondromas, CS, hemangiomas, AS</td>
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<tr>
<td>Mazabraud syndrome</td>
<td>Sporadic</td>
<td>20q13</td>
<td>GNAS1</td>
<td>Fibrous dysplasia, OS, IM myxomas</td>
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<tr>
<td>McCune-Albright syndrome</td>
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<td>20q13</td>
<td>GNAS1</td>
<td>Fibrous dysplasia, osteosarcomas, other sarcomas</td>
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<tr>
<td>Multiple osteochondromas, non-syndromic</td>
<td>AD</td>
<td>8q24, 11p11-12</td>
<td>EXT1, EXT2</td>
<td>Osteochondromas, chondrosarcomas</td>
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<tr>
<td>Multiple osseous hamartomas</td>
<td>AD</td>
<td>9p21</td>
<td>TGFBR1</td>
<td>Cartilage, bone, chondrosarcomas</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 1</td>
<td>AD</td>
<td>11q13</td>
<td>RET</td>
<td>Neurofibromas, MPNST</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2</td>
<td>AD</td>
<td>11q13</td>
<td>RET</td>
<td>Neurofibromas, MPNST</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 3</td>
<td>AD</td>
<td>11q13</td>
<td>RET</td>
<td>Neurofibromas, MPNST</td>
</tr>
<tr>
<td>Ollier disease of bone, familial</td>
<td>AD</td>
<td>11q13</td>
<td>RET</td>
<td>Chondrosarcomas</td>
</tr>
<tr>
<td>Proteus syndrome</td>
<td>Sporadic</td>
<td>-</td>
<td>-</td>
<td>Gastrointestinal, renal, skin, urogenital tumors</td>
</tr>
<tr>
<td>Rothmund-Thomson syndrome</td>
<td>AR</td>
<td>8q24</td>
<td>RECQL4</td>
<td>Osteosarcomas</td>
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<tr>
<td>Rubinstein-Taybi syndrome</td>
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<td>16p13</td>
<td>CREBBP</td>
<td>Rhabdomyosarcomas</td>
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<tr>
<td>Venous malf. With glomus cells</td>
<td>AD</td>
<td>1p21-22</td>
<td>-</td>
<td>Glomus tumors</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>AR</td>
<td>8p11-12</td>
<td>WRN</td>
<td>Bone and soft tissue sarcomas</td>
</tr>
</tbody>
</table>

SOFT TISSUE TUMORS

CLASSIFICATION

<table>
<thead>
<tr>
<th>MAJOR TYPES OF SOFT TISSUE TUMORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell type</td>
</tr>
<tr>
<td>(Myo)fibroblast</td>
</tr>
<tr>
<td>Adipocyte</td>
</tr>
<tr>
<td>Smooth muscle cell</td>
</tr>
<tr>
<td>Skeletal muscle cell</td>
</tr>
<tr>
<td>Endothelial cell</td>
</tr>
<tr>
<td>Schwann cell</td>
</tr>
<tr>
<td>Cartilage cell</td>
</tr>
<tr>
<td>Intestinal cell</td>
</tr>
<tr>
<td>Histiocyte</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
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WHO CLASSIFICATION OF BONE TUMORS

<table>
<thead>
<tr>
<th>Chondroblast</th>
<th>Chondroblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoblastoma \x200b</td>
<td>Osteoblastoma \x200b</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>\x200bChondrosarcoma \x200b</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>\x200bOsteosarcoma \x200b</td>
</tr>
<tr>
<td>Ewing sarcoma \x200b</td>
<td>Ewing sarcoma \x200b</td>
</tr>
<tr>
<td>Myxosarcoma</td>
<td>\x200bMyxosarcoma \x200b</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>\x200bSynovial sarcoma \x200b</td>
</tr>
<tr>
<td>Myeloma</td>
<td>\x200bMyeloma \x200b</td>
</tr>
<tr>
<td>Mesenchymal chondrosarcoma</td>
<td>\x200bMesenchymal chondrosarcoma \x200b</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>\x200bFibrosarcoma \x200b</td>
</tr>
<tr>
<td>GIST</td>
<td>\x200bGIST \x200b</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>\x200bLiposarcoma \x200b</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>\x200bLeiomyosarcoma \x200b</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>\x200bRhabdomyosarcoma \x200b</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>\x200bAngiosarcoma \x200b</td>
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<tr>
<td>Liposarcoma</td>
<td>\x200bLiposarcoma \x200b</td>
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<tr>
<td>Synovial sarcoma</td>
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<tr>
<td>Myeloma</td>
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</tr>
<tr>
<td>Mesenchymal chondrosarcoma</td>
<td>\x200bMesenchymal chondrosarcoma \x200b</td>
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<tr>
<td>Fibrosarcoma</td>
<td>\x200bFibrosarcoma \x200b</td>
</tr>
<tr>
<td>GIST</td>
<td>\x200bGIST \x200b</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>\x200bLiposarcoma \x200b</td>
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<tr>
<td>Leiomyosarcoma</td>
<td>\x200bLeiomyosarcoma \x200b</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>\x200bRhabdomyosarcoma \x200b</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>\x200bAngiosarcoma \x200b</td>
</tr>
</tbody>
</table>
WH0 CLASSIFICATION OF BONE TUMORS

- Ewing/PNET
- Ewing sarcoma
- Hematopoietic tumors
  - Plasma cell myeloma
- Malignant lymphoma
- Giant cell tumor
- Malignant giant cell tumor
- Notochordal tumors
  - Chordoma
- Vascular tumors
  - Hemangioma
  - Angiosarcoma
- Smooth muscle tumors
  - Leiomyoma
  - Leiomyosarcoma
- Lipogenic tumors
  - Lipoma
  - Liposarcoma
- Neural tumors
  - Schwannoma
- Miscellaneous tumors
  - Adamantinoma
- Metastatic malignancy

CLINICAL EVALUATION
- Clinical presentation
- Physical examination
- Pretreatment evaluation:
  - 1. biopsy

IMAGING STUDIES
- The ultimate goal is:
  - 1. Detecting lesions
  - 2. Giving a specific diagnosis or a reasonable differential diagnosis
  - 3. Staging the lesion

BONE TUMORS
- Conventional radiographs are still important in the diagnosis of bone tumors.
- Many tumors are site-specific.
- Many tumors have a characteristic radiographic appearance:
  1. Osteosarcoma, 18M
  2. Osteofibrous dysplasia, adamantinoma
  3. Osteoid osteoma
  4. Fibrous dysplasia
  5. Chondromyxoid fibroma
  6. Non-ossifying fibroma
  7. Bone cyst, osteoblastoma
  8. Osteochondroma
  9. Osteosarcoma
  10. Enchondroma, chondrosarcoma
  11. Giant-cell tumor
  12. Chondroblastoma

CONVENTIONAL X-RAY

QUESTIONABLE RESULTS

SUSPICIOUS FOR MALIGNANCY

BIOPSY

MRI

TREATMENT

BONE TUMORS
- The diagnosis is based on imaging and histological criteria.
Some fancy words from the world of shadows

IMAGING STUDIES

- Although imaging studies may give a reasonably accurate diagnosis on the biological potential of a lesion, there are not many lesions that may be accurately diagnosed by imaging studies alone.
- The biopsy is the gold standard for diagnosis.

BIOPSY

- Select least invasive technique that allows diagnosis (including grade):
  - Percutaneous fine needle aspiration.
  - Percutaneous core needle biopsy (blind or image-guided).
  - Incisional biopsy.
  - Excisional biopsy.

- Core biopsies yield enough material for extensive immunohistochemical stains.

Craig cutting needle with T-handled and sheath for bone biopsies

Craig needle set

Metastatic myxoid liposarcoma to liver

Osteosarcoma

24M, arm, clear cell sarcoma

MITF

S-100
BIOPSY

• Incisional biopsies are required in many cases.

SPECIAL DIAGNOSTIC STUDIES

• Many sarcomas require additional studies to confirm the diagnosis and, in some cases, to add prognostic information.

GENETICS OF CONNECTIVE TISSUE NEOPLASMS

• Numerous cancer-specific genetic alterations have been described, unfortunately almost exclusively for soft tissue neoplasms.

• Some of them (such as translocations, numerical changes, large deletions and gene amplifications) are seen at the cytogenetic level.

• Subtle changes (such as single base pair substitutions, small deletions) require molecular genetic detection.

GRADING

• Grading is an element of any current staging system.

• Correct grading requires correct histologic typing of the sarcoma, as demonstrated by the inclusion of “histologic type” as a grading variable.
GRADING

- Weak points of grading:
  - Subjective elements (number of mitoses, percent of necrosis, tumor differentiation)
  - Sampling
  - Frequent vs. rare tumors

• Any diagnostic entity has a range of malignancy.
• The grade within the overall range depends on the histologic features (cellularity, pleomorphism, mitotic activity, necrosis, etc.)

STAGING

• The stage is an estimate of the extent or dissemination of a tumor (and in the current systems includes tumor grade).
• Staging is important for planning of treatment and prognostication.
• Clinical data and imaging studies are part of staging process
• (Visceral sarcomas excluded)

GRADING-ST SARCOMAS

GRADING SYSTEM SOFT TISSUE SARCOMAS (FFCC)

<table>
<thead>
<tr>
<th>TUMOR DIFFERENTIATION</th>
<th>Score (1-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>well diff</td>
<td>1</td>
</tr>
<tr>
<td>restricted histogenetic types</td>
<td>2</td>
</tr>
<tr>
<td>point diff &amp; unendiffer. histogenesis</td>
<td>3</td>
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</table>

<table>
<thead>
<tr>
<th>MITOTIC COUNT</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9/10HPF</td>
<td>1</td>
</tr>
<tr>
<td>&gt;10/10HPF</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20 HPF</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TUMOR NECROSIS</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>1</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>2</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>HISTOLOGIC GRADE</th>
<th>Sum of scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2 or 3</td>
</tr>
<tr>
<td>3</td>
<td>4 or 5</td>
</tr>
</tbody>
</table>

GRADING- ST SARCOMAS

DIFFERENTIATION SCORE 1
- Well differentiated sarcoma (fibro-, lipo-, leiomyo-, chondro-)
- Well differentiated MPNST (neurofibroma with malignant transformation)

DIFFERENTIATION SCORE 2
- Conventional fibrosarcoma, leiomyosarcoma, angiosarcoma
- Conventional MPNST
- Myxoid sarcomas (MFH, liposarcoma, chondrosarcoma)
- Storiform-pleomorphic MFH

DIFFERENTIATION SCORE 3
- Sarcomas of undefined histog. (ASPS, SS, ES, CCS, undiff. Sarc., malig. rhabdoid tumor)
- Ewing family of tumors
- Pleomorphic sarcomas (lipo-, lei-)
- Round cell and pleomorphic liposarcoma
- Rhabdomyosarcoma (except botryoid and spindle cell)
- Poorly differentiated angiosarcoma
- Triton tumor, epithelioid MPNST
- Extraskeletal mesenchymal CS, and osteosarcoma
- Giant-cell and inflammatory MFH

STAGING (G-TNM)- ST SARCOMAS

| STAGE GRADE PRIMARY TUMOR LYMPH NODES METASTASES |
|-------------------------------------------------|---------------------------------|
| IV / Tumor grade / MEAS/CM, or TE>7CM | MEAS/POS ABSENT/PRE |
| IA / Low / T1a or T1b | NEGATIVE ABSENT |
| IB / Low / T2a or T2b | NEGATIVE ABSENT |
| II A / High / T1a or T1b | NEGATIVE ABSENT |
| IIB / High / T2a | NEGATIVE ABSENT |
| III / High / T2b | NEGATIVE ABSENT |
| IV / Any / Any | POSITIVE OR NEGATIVE PRESENT |

"a" superficial tumors of trunk and extremities (above fascia)
"b" deep tumors of trunk and extremities or intra-abdominal, intra-thoracic or retro-peritoneal
STAGING OF ST SARCOMAS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>66%</td>
</tr>
<tr>
<td>II</td>
<td>72%</td>
</tr>
<tr>
<td>III</td>
<td>52%</td>
</tr>
<tr>
<td>IV</td>
<td>10-20%</td>
</tr>
</tbody>
</table>

5-yr survival

STAGING OF ST SARCOMAS

NEJM 2005; 353: 701-711

BONE TUMORS

Stage IA: T1 N0, NX M0 Low grade
Stage IB: T2 N0, NX M0 Low grade
Stage IIA: T1 N0, NX M0 High grade
Stage IIB: T2 N0, NX M0 High grade
Stage III: T3 N0, NX M0 High grade
Stage IVA: Any T N0, NX M1a Any grade
Stage IVB: Any T N1 Any M Any grade


BONE SARCOMAS

• Like ST sarcomas, bone sarcomas need to be graded (grading is an important element of the staging and determines if the tumor is stage I or II).
• The TNM system for bone sarcomas follows a 2 tier grading system: low- and high-grade.

BONE TUMORS

• Stage I: low grade intra-compartmental (risk of metastasis <25%)
• Stage II: high-grade extra-compartmental (risk of metastasis >25%)
• Stage III: any grade, discontinuous tumor in the primary bone site
• Stage IV: any grade, metastatic

PARAMETERS TO BE INCLUDED IN REPORT OF A SARCOMA

• FINAL REPORT
  – 1. Tumor site, type of excision
  – 2. Depth of the tumor
  – 3. Tumor type and variant
  – 4. Grade (if possible)
  – 5. Tumor size
  – 6. Status of margins & L.N.
  – 7. Percent of necrosis
  – 8. Vascular invasion

BONE TUMORS

• The staging of bone sarcomas follows the TNM system.

TREATMENT

- Surgery and pre- or postoperative external beam radiation treatment in the primary local treatment for most patients with localized disease.
- Adjuvant chemotherapy is usually reserved for patients with high-grade sarcomas.
- Patients with metastatic disease considered for chemotherapy and selected cases may undergo metastasectomy.

TREATMENT

- Currently approximately 90% of patients with localized extremity sarcomas undergo limb-sparing surgery.