Sarcomas

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This outline provides an overview of sarcomas. The goal is to acquire knowledge about the general principles of diagnosis and treatment. Information on the more common type of sarcomas is presented. Additional information is available for all types of sarcoma via the links listed at the end of this section. Also, the majority of the information relates to an adult population. Information on pediatric sarcomas may be retrieved via the links listed at the end of this section.

Cell of Origin

- From ***mesodermal*** tissues (muscle, bone, vascular and fibrous tissues)

NB. Most cancers are carcinomas and arise from epidermal or endodermal tissues.

Major and Important Subtypes

- Osteogenic sarcoma
- Soft tissue sarcomas
- Rhabdomyosarcomas
- GISTs (Gastrointestinal Stromal Tumors)

Incidence and Mortality

- 284 “bone sarcomas” and 887 “soft tissue sarcomas” were diagnosed in 2003 (approximately 1% of all new cancers diagnosed)
- 134 individuals died of “bone sarcomas” and 346 of “soft tissue sarcomas” (last year specific data for sarcomas available from Cancer Statistics.)

- in 2007 159,000 new cases of cancer
  72,700 deaths due to cancer

Soft Tissue Sarcomas

Predisposing conditions:

- Von Recklinghausen’s disease (neurofibromatosis)
- Gardner’s syndrome
- Werner’s syndrome
- Tuberous sclerosis
- Basal cell nevus syndrome
- Li-Fraumeni syndrome (p53 mutations).

Location of sarcomas:

- 50% arise in the extremities, 40% in the retroperitoneum and 10% in the head and neck

Cellular classification:

- by cell of origin
- 40% are MFH (malignant fibrous histiocytoma) and are most common
- 25% are liposarcomas

- GIST tumors are unique and have a special treatment
  - Immunohistochemicallly different from leiomyosarcomas
  - CD34 and CD117 (c-kit) positive
  - CD 117 more common in malignant vs benign GISTs
  - Stomach GISTS are malignant if > 5-10 cm, have a high mitotic index or metastases
  - Small bowel GISTs are malignant if there are mitoses or > 2 cm

- histologic grade reflects the metastatic potential more accurately than cell type. Criteria for grade include:
  - number of mitoses per high-powered field
  - presence of necrosis
  - cellular and nuclear morphology
  - degree of cellularity

Staging

- Includes grade, size of primary, nodes and spread to distant sites
- Nodal involvement is rare (3%)
- CT chest to screen for distant metastases recommended for tumors > 5 cm or moderate to poor differentiation (grade 2 – 4)

- Grade
  - GX: grade cannot be assessed
  - G1: well differentiated
  - G2: moderately differentiated
  - G3: poorly differentiated
  - G4: poorly differentiated or undifferentiated
- Primary Tumor (T)
  - TX: Primary tumor cannot be assessed
  - T0: No evidence of primary tumor
  - T1: Tumor $\leq$ 5 cm in greatest dimension
  - T2: Tumor > 5 cm in greatest dimension
  - “a” is appended for tumors above the superficial fascia.

- "b" is appended for deep tumors defined as either below the superficial fascia or invading the superficial fascia.
- Retroperitoneal, mediastinal and pelvic sarcomas are considered deep tumors.

- Regional Lymph Nodes (N)
  - NX: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastases
  - N1: Regional lymph node metastases (NB UICC stage IV)
- Distant Metastases (M)
  - MX: Distant metastases cannot be assessed
  - M0: No distant metastases
  - M1: Distant metastases

- UICC Staging

  - Stage I
    - Low grade (G1 or G2),
    - T1 or T2 either a or b
    - and N0 and M0

  - Stage II
    - High grade (G3 or G4)
    - T1 (a or b) and T2a
    - N0 and M0

  - Stage III
    - High grade (G3 or G4)
    - T2b (large and deep)
    - N0 and M0

  - Stage IV
    - Metastases to nodes or distant sites

Prognosis

- Related to: Patient age
  Size of tumor
  Histologic grade
  Stage of tumor
- Poor prognostic factors:
  Age > 60 years
  Tumors > 5 cm
  High grade histology (high mitotic rate, presence of hemorrhage and necrosis)

Principles of Diagnosis and Management

- Adequate core-needle or incisional biopsy to determine histological type and tumor grade.
- Initial biopsy requires planning to avoid compromising subsequent curative resection
- Treatment is determined by the grade of the tumor

- Requires multidisciplinary team of cancer specialists

- Enroll in a clinical trial whenever possible

Principles of Surgery

- *For high grade soft tissue sarcomas of the extremities*
  - Combined-modality with preoperative or postoperative radiation to reduce local recurrence
  - Use wide margin function-sparing excision to preserve functional extremity

- *For high grade soft tissue sarcomas of the trunk and head and neck*
  - Combined-modality with radiation therapy +/-chemotherapy

- *For retroperitoneal*
  - Remove all gross disease and spare viscera not invaded by tumor
  - Prognosis poorer as difficult to completely resect and limits on high-dose radiation
  - Prospective randomized trials have shown no benefit for pre-operative or post-operative chemotherapy.

- *For GISTS*
  - Surgery is the most effective.
  - For unresectable disease use Imatinib mesylate (tyrosine kinase inhibitor) (Gleevac) to produce a sustainable tumor response

- *For metastatic disease to lung*
  - When optimal biologic behaviour (few metastases, long disease-free interval, slow clinical growth)

- *Mohs surgical technique*
  - for small well-differentiated sarcomas
  - when cosmetic results are considered to be very important

Principles of Radiation Therapy

- May be given pre-operatively or post-operatively
- To reduce risk of local recurrence
- To reduce size of mass to reduce extent of surgery required (eg. Amputation) or to permit resection

Principles of Chemotherapy

- *No single randomized trial has shown benefit for adjuvant chemotherapy as:*
  - Small number of patients per trial
  - Different therapeutic regimens and drug doses
  - Different tumor sites
  - Different tumor grades

- *Quantitative meta-analysis*
  - 1568 patients
  - 14 trials of doxorubicin based therapy
  - 6% improved local relapse-free interval
  - 10% improved for distant relapse free interval
  - 10% for recurrence-free survival
  - No overall survival benefit at 10 years

- Patients with high grade tumors should be enrolled in **clinical trials**

Management of Stage I

- Low metastatic potential
- May recur locally if inadequately resected
  - Require negative tissue margins of $\geq$2 cm in all directions

- Radiation therapy with a shrinking field technique may be beneficial for unresectable or resectable tumors where:
  - High risk of residual disease
  - Margins are known to be < 2 cm
  - Wider resection would require amputation or removal of a vital organ
  - For unresectable, use high-dose preoperative radiation therapy followed by surgical resection and postoperative radiation therapy

- For tumors of the retroperitoneum, trunk, and head and neck
  - Surgical resection with postoperative radiation therapy if negative margins cannot be obtained.
  - Preoperative radiation therapy followed by maximal surgical resection.

- As low risk of metastasis, chemotherapy is not used

Management of Stage II & III

- Increased potential for metastatic spread

- *Extremities*
  - Limb-sparing surgery comparable to amputation
  - Requires wide surgical resection and either pre or post operative radiation therapy
  - In some cases use chemotherapy
  - For marginally resectable use radiation therapy and chemotherapy prior to surgery so can have limb preservation and follow with post-operative radiation
  - Patients with high-grade tumors (Grades 3 or 4) > 5 cm are eligible for prospective clinical trials of adjuvant chemotherapy

- *Retroperitoneum*
  - Local recurrence is the most common cause of death
  - Role of adjuvant radiation therapy not clearly defined, but, often given to decrease risk of local recurrence as very difficult to get clear and adequate margins
  - Prospective randomized trials have not shown improved survival with preoperative or adjuvant chemotherapy for this subgroup again due to small numbers of patients etc in the trials.

Management of Stage IV

- *Nodal disease*
  - Synovial cell sarcomas, epithelioid sarcomas, and rhabdomyosarcomas most frequently have nodal involvment
  - Local control of the primary tumor is best obtained by resection with negative margins, lymphadenectomy when appropriate and postoperative external beam radiation
  - In some centers, radiation therapy may be used prior to and following surgical extirpation
  - Adjuvant chemotherapy may be considered for patients eligible for clinical trials.

- *Visceral disease*
  - Surgery with curative intent is possible for patients with limited pulmonary metastases
  - Role of adjuvant therapy for pulmonary nodules is under clinical evaluation
  - Value of resection of hepatic metastases in unclear
  - Only doxorubicin and ifosfamide as singe agents show a > 20% response rate

- Other agents – dacarbazine, cisplatin, methotrexate and vinorelbine
- For older patients use sequential single agents
- High-dose chemotherapy has not influenced disease-free or overall survival

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Osteogenic Sarcoma of Bone

Epidemiology

- Occurs predominantly in adolescents and young adults
- ~5% of all tumors in childhood

- 50% occur around the knee

- Natural history has not changed
  - < 30% survive free of relapse if only treated with surgery
  - > 50% develop metastases within 6 mos of surgery
  - ~90% developed recurrent disease within 2 years of diagnosis

Pathology

- Two major sub-groups
  - Central (medullary)
  - Surface (peripheral)

- Central (medullary) types
  - Conventional central osteosarcoma
  - Telangiectatic osteosarcoma
    - May be confused with aneurismal bone cyst but approach is for conventional osteosarcoma
  - Intraosseous well-differentiated (low-grade) osteosarcoma
    - Very favourable prognosis and treatment is radical excision alone
  - Small cell osteosarcoma

- Surface (peripheral) types
  - Parosteal (juxtacortical) well-differentiated (low-grade) osteosarcoma
  - Periosteal osteosarcoma: low-grade to intermediate-grade osteosarcoma.
  - High-grade surface osteosarcoma

- Most common is conventional central osteosarcoma
  - Microscopically has areas of necrosis, atypical mitoses, and malignant osteoid tissue and/or cartilage

- Extraosseous osteoscaroma
  - Treat as soft tissue sarcoma

Stage

- 2 subgroups
  - Localized
  - Metastatic

- Localized
  - Limited to the bone of origin
    - Local skip-metastases within bone has a poorer prognosis
  - Common sites in descending order
    - Tibia, humerus, pelvis, jaw, fibular and ribs
  - Head an neck is more likely to be low-grade while appendicular skeleton more likely to be of higher grade and occurs in older patients

- Metastatic
  - 10-20% at diagnosis
  - 85-90% metastatic to lung
  - Second most common site is bone
    - Multiple bone metastases has an extremely grave prognosis

Prognostic Factors

- Site of disease
  - Axial skeleton have greatest risk of progression and death
  - Pelvic osteosarcomas have overall survival rate of 20 – 47%
- Resectability
  - Very resistant to radiation therapy
- Patient age
- Tumor volume
- Histologic subtype
- Degree of histologic necrosis following induction chemotherapy
  - > 95% has a better prognosis than those with lesser amounts of necrosis
- Prognosis is the same for second malignancy neoplasm as primary malignancy

Management of Localized Disease

- Biopsy should be performed by the surgeon who will do the definitive operation since incision placement is crucial

- Localized, completely resectable high-grade osteosarcoma
  - Neoadjuvant chemotherapy followed by extirpative surgery (amputation, limb salvage, or rotationplasty) and postoperative adjuvant chemotherapy

- Unresectable lesions
  - Currently trial of intensive combination chemotherapy and high-dose, very well collimated localized radiation.

- MFH
  - Wide local excision is recommended regardless of tumor grade.
  - Preoperative chemotherapy may be required to achieve wide local excision
  - Complete surgical resection is crucial BUT 80% will develop metastatic disease without adjuvant chemotherapy
  - Overall relapse-free survival ranges from 50-75% with adjuvant chemotherapy and complete surgical resection of primary tumor

- Amputation vs Limb-sparing Surgery
  - No difference in overall survival
  - Amputation has a lower local recurrence rate
  - One randomized trial - no difference in disease-free survival for preoperative chemotherapy vs. immediate surgery followed by adjuvant chemotherapy
  - Limb-sparing surgery done when wide surgical margins possible
  - 80% of extremity osteosarcomas can be treated by limb sparing operation

- Pathologic fracture at diagnosis or during preoperative chemotherapy
  - Limb-sparing surgery done when wide surgical margins can be achieved
  - Consider immediate amputation when inadequate margins especially if poor histologic response to preoperative chemotherapy

Management of Metastatic Disease

- Progression-free survival rate for patients with metastatic osteosarcoma is approximately 20%
  - Pulmonary metastatic disease has best survival
  - Multi-focal bone disease has extremely poor prognosis
  - Chemotherapy and aggressive surgical resection may achieve significant life prolongation

- Multifocal osteosarcoma
  - Classically presents with symmetrical, metaphyseal lesions
  - May be difficult to decide which is the primary lesion
  - More conventional presentation is large primary lesion and “skip lesions”
  - Prognosis is poor
  - Surgical removal of primary and all metastatic disease at the time of diagnosis or after intensive multi-agent regimens is necessary

Management of Recurrent Disease

- Most common is lung
  - May be cured with surgical resection +/- chemotherapy
  - Better outcome if
    - solitary pulmonary nodule,
    - unilateral lung involvement,
    - longer interval from initial diagnosis,
  - Patients with unilateral nodules may benefit from bilateral exploration as study found lesions in contraleteral lung not identified by CT scan

- 5-year survival rate of 20-45% following complete resection of metastatic pulmonary tumors and 20% following complete resection of metastases at other sites

- Unresectable metastatic disease survival is < 5%
  - Observation only after resection of metastatic disease has a poor overall and disease-free survival

- Outcome of local recurrence worse than metastatic disease

- Role of chemotherapy
  - Standard chemotherapy regimens for osteosarcoma is active in approximately 1/3 patients who have not had previous chemotherapy
  - Peripheral blood stem cell transplantation has not been of benefit

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Rhabdomyosarcoma

Definition

- Malignant tumor of skeletal muscle

Epidemiology

- ~3.5% of the cases of cancer in children 0 -14 years
- 2% of cases in adolescents & young adults 15-19 years.

Overview of Disease

- Curable disease with combined modality
  - > 70% survive 5 years
- Most common primary sites
  - head and neck, (eg paramenigeal, orbit, pharyngeal etc),
  - genitourinary tract,
  - extremities

- Most cases occur sporadically
- Small proportion associated with:
  - Li-fraumeni,

- neurofibromatosis type I,
- Beckwith-Wiedemann syndrome

Histopathology

- Embryonal
  - Most common – 60-70% in children
  - Common sites - head an neck; genitoruinary
  - Two types – Alveolar and Pleomorphic
    - 20% of alveolar have an increased frequency in adolescent
    - Pleopmorphic occurs 30-50 years and is rarely seen in children

- Botryoid
  - 10% of all
  - Are embryonal tumors
    - under the mucosal surface of body orifices
    - Common sites are vagina, bladder, nasopharynx, and biliary tract

- Spindle cell
  - Most frequent in the paratesticular site

- Botryoid and spindle cell are associated with a very favorable outcome

Staging

- Stage 1
  - 13% of all patients
  - Localized disease and favourable sites:
    - orbit;
    - head and neck (excluding parameningeal sites),
    - genitourinary (excluding bladder/prostate),
    - biliary tract (favorable sites)

- Stage 2
  - ~ 20% of all patients
  - Localized disease not in stage 1 (unfavorable sites)
  - Primary tumors $\leq$ 5 cm
  - No clinical regional lymph node involvement
  - IIA grossly resected tumor, microscopic residual disease, no lymph nodes
  - IIB complete resection of local disease including lymph nodes
  - IIC gross resection of local and regional lymph nodes disease

- Stage 3
  - ~48% of all patients
  - Localized disease of any other primary site.
  - Differ from stage 2 as tumor > 5 cm and/or regional node involved

- Stage 4
  - ~18% of all patients
  - Metastatic disease at diagnosis

Prognostic Factors

- Extent of disease following primary surgical procedure
  - Clinical group III – gross residual disease - ~ 70% 5-year survival
  - Clinical group II – microscopic residual tumor - ~ 80% 5-year survival
  - Clinical group I – no residual disease – 90% 5 year survival

- Low risk
  - Localized embryonal at favorable sites (i.e. stage 1) (Groups I, II, and III)
  - Embryonal at unfavorable sites with either complete resection or microscopic residual disease

- Intermediate risk
  - Embryonal at unfavorable sites with gross residual disease (Group III)
  - Metastatic embryonal < 10 years
  - Non-metastatic alveolar or undifferentiated at any site

- High risk
  - Metastatic disease or undifferentiated excepting embryonal < 10 years

Principles of Management

- Basic principle in children
  - complete surgical resection with a margin of normal tissue and lymph node sampling of the draining nodal basin

- For microscopic residual tumor following initial excision
  - re-excision of the primary tumor bed prior to the initiation of chemotherapy

- Head and Neck
  - Wide excision where feasible and ipsilateral neck lymph node sampling
  - Narrower resection margins (<1 mm) are acceptable if anatomic restrictions
  - Must consider cosmetic and functional factors
  - Multidisciplinary approach required for the nasal area, paranasal sinuses and temporal fossa
  - Unresectable disease is managed with chemotherapy and radiation therapy
  - Orbital disease is biopsied prior to chemotherapy and radiation therapy

- Extremities
  - Requires wide local excision with removal en bloc of a cuff of normal tissue
  - Amputation may be required for extracompartmental lesions involving major neural and/or vascular structures in addition to the muscle of origin

- Extensive pretreatment assessment for regional nodal involvement is warranted due to therapeutic and prognostic significance
- Sentinel lymph node mapping may be used but role is not determined

- Truncal
  - Chest wall and abdominal wall lesions are managed with wide local excision and an attempt to achieve negative microscopic margins
  - Very large truncal masses are biopsied prior to neoadjuvant chemotherapy and/or radiation therapy and then surgical resection
  - Most patient have disease which is amenable to complete resection with negative margins and hence associated excellent long-term survival

- Intrathoracic or intra-abdominal disease
  - Rarely resectable due to massive size or involvement of vital organs
  - May be resectable after chemotherapy
  - Survival advantage - 73% vs 34-44%

- Genitourinary
  - Salvage of bladder is an important goal

  - Surgical resection is usually done after chemotherapy and radiation to reduce bulk of disease. 3 yr survival is 90%

Treatment by Risk Categories

- Low risk
  - Maintaining high survival rate (< 90%) while minimizing the long-term consequences of chemotherapy is essential
  - Favorable prognosis is defined as:
    - embryonal rhabdomyosarcoma occurring favorable sites (is Stage 1)
    - embryonal occurring in favorable sites with either completely resected (i.e. Group1) or microscopic residual disease

- Intermediate risk
  - Survival rates from 55 – 70%
  - VAC chemotherapy is standard treatment (vincristine, dactinomycin, and cyclophosphamide)

- High risk
  - Have a poor prognosis with current therapy

FOR FURTHER READING

http://www.cancer.gov/cancertopics/types/soft-tissue-sarcoma/

http://www.cancer.gov/cancertopics/types/bone/

http://www.cancer.gov/cancertopics/types/childrhabdomyosarcoma/

http://www.cancer.gov/cancertopics/types/ewings/

http://www.cancer.gov/cancertopics/types/uterinesarcoma/

http://www.emedicine.com/med/ONCOLOGY.htm

http://www.lhsc.on.ca/priv/library/
This site has access to most major medical journals and textbooks. Up-To-Date an excellent resource is available via this site.