ANSWERS AND ADDITIONAL INFORMATION FOR ORTHOPAEDIC CLINICAL QUIZ
SKELETAL AND EXTRA-SKELETAL TUMOURS REVISITED

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Quiz 1

a. A typical chronic non-healing ulcer with two abnormal findings: roll-out ulcer edge and nodular lesions in scarred tissue, may indicate malignant transformation to either squamous cell carcinoma (SCC) of the skin or osteosarcoma of the bone.
b. SCC arising from chronic non-healing osteomyelitis (Marjolin ulcer) is the most likely diagnosis based on the presence of roll-out edge and symptom of pain is probably due to perineural invasion of the tumour (skin nodules). Plain radiographs show chronic OM changes without evidence of tumor osteoid formation. Gross prosection specimen of the excised tissue indicates typical chronic osteomyelitic bone.
c. Four-quadrant biopsy or punch biopsies of the ulcer margin for histological examination. A Marjolin ulcer typically lacks basement membrane and should be differentiated from another pre-malignant lesion, squamous pseudoepitheliosis.
d. Following a wide resection margin which includes either intercalary segment of the tibia or proximal tibia, normal soft tissue and 6cm normal skin around the ulcer, a large defect is created. By considering a wound bed previously containing an infected tissue and proximity of resection margin to the meta-epiphyseal junction, a staged combined reconstruction using a vascularized free flap and megaprosthesis arthroplasty or knee fusion allograft is preferred. If joint-preservation intercalary resection is feasible, a staged procedure consisting of free flap and defect filling with bone cement to initiate the initial stage of membrane-induced osteosynthesis is an option. The bone is stabilized with either circular external fixator or antibiotic-coated locked nail. In the second stage, bone cement is removed through an incised membrane and the defect is reconstructed with either cancellous bone graft or bone graft substitute. This technique is known as membrane-induced osteosynthesis of Masquelae.

SQUAMOUS CELL CARCINOMA (SCC) ARISING FROM CHRONIC PRE-EXISTING LESIONS

Although the association between chronic burn scar and delayed malignant transformation was documented by Celsus 2000 years ago, Jean Nicolas Marjolin (1828) was credited for observing and classifying cellular changes 'ulcer cancroide' in burned skin. Today, the lesion that bears the eponym Marjolin ulcer is interchangeably used to any malignant neoplasm that show similar histology to SCC arising in association with a variety of pre-existing chronic precursor lesions: scars including burned scars and vaccination scars, draining sinus of Chronic OM and pilonidal sinus, and venous ulcers.

The pathophysiology of Marjolin ulcer is presumed to involve a two-step process of initiation phase of formation of dormant neoplastic cells in an immunologically privileged site of relatively ischaemic and dense scar tissue with fragile epithelium and promotion phase into active neoplasm after exposure to repeated injuries or stimulation by co-carcinogens leading to cell mutation and eventual neoplasm. This transformation occurs in less than 5% of such lesions, typically after a latency period of 20-40 years of exposure to mutagenic hits/carcinogenic stimuli in pre-existing precursor lesions. The co-carcinogens include toxin released from repeatedly damaged tissue by trauma, infection and UVL from sun exposure. However, acute variant of Marjolin ulcers developing rapidly within few months to years have been described. Progression into SCC can be delayed by avoiding or minimizing these carcinogenic stimuli. Most Marjolin ulcers evolved in the settings of burn scars (75%), traumatic non-healing wounds (8%), venous ulcers (6%), pressure ulcers (3%), and chronic osteomyelitis (1.5%).

The malignant ulcer appears irregular, pink- or white-tan firm mass often with fungating surface surrounding or adjacent to an easily identifiable draining sinus. Many present as increasing local pain or drainage with foul odour or bleeding and skin changes in-forms of new nodular lumps and role-out ulcer edge or pathological fracture. This secondary SCC displays an aggressive clinical behavior. Perineural invasion (2.4%-14%) typically manifests as increasing pain, has a prognostic implication. Metastasis disease to regional nodes (22-25%) before distant visceral organs (6-14%) develops within 18 months of initial diagnosis/resection (unusual after 3 years). The 5-year survival rate for Marjolin ulcer is worse than conventional SCC (52% versus 85%) and it is attributable to frequent under-diagnosis, lack of vigilance and inadequate treatment in form of non-radical treatment. Distant metastasis poses poor prognosis with a 3-year survival rate of 35-50%.

Radiographically, with background of COM features (lytic or mixed lytic-sclerotic bone lesion with surrounding bone sclerosis and cloaca), the initial lesion appears bland before extending into the bone to manifest with a more aggressive destruction. However, tumour bone permeation and fibrosis due to osteomyelitis is difficult to distinguish. MRI show low and partial signal on T2-weighted images with mild reactive bone marrow edema pattern, contrast enhancement in the sinus tract, and malignant transformation.

The differential diagnoses include non-neoplastic lesions: chronic OM and pseudoepitheliomatous hyperplasia, and neoplastic lesions: basal cell carcinoma, osteosarcoma and plasmacytoma. Cultures from draining sinuses and deep tissue are important for microbiologic diagnosis. Four-quadrant biopsies of ulcer or multiple punch biopsies of suspicious area and bone biopsy are equally important to improve diagnostic yield. Identification of squamous cell markers by immunocytohistochemical studies (cytokeratin 5/6, p63, high molecular weight keratin) may be needed. Histologically, the ulcer or sinus tract is lined by squamous epithelium and it may show a continuum of benign lesion (squamous hyperplasia, low- to high-grade dysplasia without invasion) and malignant (well differentiated SCC with keratin pearls and intercellular keratin bridges, poorly differentiated without keratinization or intercellular bridges, basement membrane disruption by tumor invasion) changes with background COM changes. Pseudoepitheliomatous hyperplasia is a SSC mimicker representing reactive squamous metaplasia that may gradually transform to full-blown SSC after invading basement membrane of the epithelium. Sentinel node biopsy of the draining regional nodes has recently been advocated. Once the diagnosis is established, consider multidisciplinary therapy (MDT): cryotherapy, radiotherapy, Mohs micrographic surgery, wide excision with/without reconstruction as per case basis depending on staging and tumor location.

Staging

Primary Tumor Extent (T)		**Regional Nodes (N)**	
Tx	Can't be evaluated	Nx	Can't be evaluated
T0	No evidence of primary tumor	N0	No regional node involvement
Tis	Carcinoma in situ	N1	Regional nodes involved
T1	Primary tumor longest axis <2cm	**Metastasis and Distant Node (M)**	
T2	Primary tumor >2cm and <5cm	Mx	Can't be evaluated
T3	Primary tumor longest axis >5cm	M0	No distant metastasis and node
T4	Extension to bone and/or rmuscle	M1	Distant metastasis present

An aggressive surgical approach has become the gold standard management for Marjolin ulcers. In principle, surgical excision of a SCC recommends 4mm margin for lesion of <2cm diameter and at least 6mm margin for lesion of >2cm diameter if 95% cure rate is targeted. Amputation with or without regional node dissection is recommended for SCC arising in a draining sinus of COM. The decision for en block lymph node clearance is based on sentinel node staging: sub-capsular, sub-capsular and parenchymal, parenchymal and extensive parenchymal patterns. Owing to the nature of this carcinoma in poorly vascularized scar tissue, the role of adjuvant chemotherapy and radiation therapy remains controversial. In cases with metastatic disease or tumour at surgically non-feasible site, chemotherapy with or without radiation therapy is recommended.

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Quiz 2

a. An eccentric predominantly lytic with few incomplete trabecula bone lesion of narrow transitional zone involving meta-epiphyseal region of the distal femur. The lesion has breached the anterior and posterior cortices of the distal femur. However MRI displays a pathologic lesion containing fibroblastic stroma with variable mineralization.
b. Considering a slow onset disease of non-progressive clinical behavior, the lesion with these imaging findings is probably representing a variant of osteosarcoma called central low-grade osteosarcoma.
c. Tumour staging involves imaging studies and tissue biopsy. Imaging studies help to determine local extension (MRI of the effected limb) and distant metastases in the lungs (plain radiograph and CT thorax) and other bones (bone scans). Representative tissue biopsy is essential for tumour grading. A stage-IB disease (low grade tumour with local extension or extra-compartmental disease) is the most likely surgical pathological stage.
d. Although regarded as a low-grade malignancy, wide margin resection remains the preferred option as inadequate resection is often associated with high rate of local recurrence displaying a higher histological grade with metastatic potential. Due to tumour proximity to the knee involving the epiphysis with cortical breaching, tumour excision requires osteochondral resection of the distal-third of the femur along with cuff of normal soft tissues. Reconstruction options include

tumour megaprosthesis arthroplasty, knee fusion allograft and van Nes rotationplasty. For young adult with expectant optimum functional demand, megaprosthesis arthroplasty is the best option. As the tumour is responds to neither chemotherapy nor radiotherapy, the role of pre- and post-operative adjuvant chemotherapy remains controversial or unnecessary until adequate supportive data are available from large RCTs

LOW-GRADE CENTRAL OSTEOSARCOMA

Distinct variants of osteosarcomas (OS) based on their anatomic site of origin: medullary cavity or periosteal tissue adjacent to the metaphyseal surface of a long bone, and their histological sub-types: high-grade and low-grade malignancy, have been described. Rare anatomic variants with exclusive intra-cortical confinement or extraskeletal site have also been encountered. The majority of high-grade variants are conventional central medullary (90% of all OS), telangiectatic and extra-skeletal OS. Surface parosteal OS are typically low-grade and periosteal OS are frequently intermediate-grade. However, low-grade variants of central and extra-skeletal OS as well as high-grade variants of surface OS have also been reported.

Low-grade central OS (LGCOS) variant is regarded as a medullary-equivalent or homologue of parosteal OS because of its fibroblastic predominant resemblance. This rare variant accounts for 1-2% of all OS. It has predilection for a decade older patients and with longer symptoms build-up in contrast to the conventional OS. The difficulty in establishing the diagnosis remains the key problem.

Radiographically, it may mimic mono-ostotic fibrous dysplasia, desmoplastic fibroma, nonossifiying fibroma, osteoblastoma and aneuysmal bone cysts. It appears as a more permeative lesion into the fatty marrow and native bone trabeculae, and less homogenous in comparison to ground glass appearance of fibrous dysplastic lesion. If osseous matrix is scant, it may mimic a desmoplastic fibroma. Andresen et al. (2004) described four radiological types of LGCOS: type 1- lytic with variable coarse and thick trabeculae, type 2- predominantly lytic with few thin incomplete trabeculae, type 3- densely sclerotic, and type 4- mixed lytic and sclerotic.

Grossly, it is well-demarcated whitish firm mass of fibrous whorled appearance centred in the medullary cavity of the metaphysic or meta-diaphyseal region with soft tissue component in some cases. Histologically, it may be indistinguishable with benign fibrous lesions particularly fibrous dysplasia and desmoplastic fibroma. A permeative growth pattern is absent in fibrous dysplasia and desmoplastic fibroma lacks matrix production. It consists of parallel trabeculae as round islands woven bone intimately intermingling with mild-to-moderate bland neoplastic spindle cells with variable amount of osteoid production and fibrous stroma resembling fibrous dysplasia if involving the medullary canal. However, its trabeculae are longer and parallel in contrast to short and curly trabeculae of fibrous dysplasia. The spindle cells show low mitiotic activity and mild atypia. Immunohistochemical stains with cycline-dependant kinase 4 (CDK4) and murine double-minute 2 (MDM2) help to aid the diagnosis of LGCOS. Despite this difficult differentiation with benign lesion, distinguishing low-grade central OS from high-grade surface parosteal OS variant and other benign fibrous lesions remains crucially important as this will influence surgical decision.

In general, low-grade central OS has significantly better prognosis than conventional OS. With an expected 90% disease-free at both 5 and 10 years, LGCOS is an eminently curable malignant tumour with appropriate treatment. Treatment with surgery in-form of wide local resection with clear margin alone is adequate. Adjuvant chemotherapy or radiotherapy is not routinely necessary. Local recurrences in-form of high-grade malignancy and metastatic diseases are typically delayed for 5-10 years and are frequently related to inadequate surgical margins.

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Quiz 3

a. Differential diagnoses should consider lesion arising from muscle (heterotopic ossification), synovial lining (tophaceous gouty synovitis, tuberculous synovitis and synovial sarcoma), bone or soft tissue (osteosarcoma).
b. Lesion with exclusive confinement in the hypothenar area may exclude synovial-related diseases owing to the pertinent anatomy of the synovial bursae in the palmar aspect of the hand. Plain radiograph and MRI display a large soft tissue tumour with irregular mineralization of inverted zonal phenomenon rather than peripheral zonation pattern. This would exclude heterotopic ossification. The lesion seems to arise from the soft tissue and encircling the fifth metacarpal rather than arising from the bone and forming an extensive soft tissue component without destruction of the cortex. However, tissue biopsy is all that is needed to solve these puzzling differentials. Extraskeletal or soft tissue osteosarcoma is the likely diagnosis.
c. Compression or entrapment neuropathy of the ulnar nerve as evidenced by the presence of ulnar claw hand.
d. Wide local resection including amputation to achieve negative margins has been considered as the preferred option as systemic chemotherapy has previously been presumed to give unfavorable response. With recent data indicating an improved overall prognosis associated with multimodal treatment including multi-agent chemotherapy regimens followed by surgery (limb salvage or amputation), EOS is best treated similar to conventional OS

EXTRA-SKELETAL OSTEOSARCOMAS (ESOS)

ESOS is a high-grade malignant bone-producing neoplasm arising exclusively in the muscle or soft tissue without attachment or relation to underlying bone. Despite extremely rare, low-grade variant of ESOS showing similar histology to parosteal osteosarcoma and well-differentiated central low-grade OS have been reported.

The clinical features of ESOS are not well documented as they are rare tumors accounting for less than 5% of all OS. They affect patients of age later than bony OS i.e. middle-aged adults of older than 40 years of age with male-to-female ratio of 2:1 and manifest as slowing growing occasionally painful deep-seated mass of more than 5cm. Differential diagnoses include acute osteomyelitis or deep-seated inflammatory phlegmon and heterotopic ossification A post-irradiation ESOS may develop following local radiation therapy on pre-existing pathology.

Imaging studies commonly display an ill-defined large soft tissue density of >5cm with irregular calcification most often central (inverted zonal phenomenon as oppose to peripheral zonation in heterotopic ossification)

Grossly, ESOS is a circumscribed non-encapsulated mass which appears tan fleshy tumour with areas of haemorrhage and necrosis. It is histologically characterized by highly cellular pleomorphic neoplastic cells with polygonal, epitheloid or spindle shape and prominent mitotic activity. The tumour contains lacelike osteoid ramifying between individual cells or small clusters of cells and matured mineralized bone mainly in central location. Hyaline cartilage with endochondral ossification may present (positive staining for S-100) when chondrocytes show atypia. Area with necrosis may occasionally have osteoclast-like giant cells. Histologically, differential diagnoses include conventional OS with soft tissue extension, dedifferentiated liposarcoma and undifferentiated pleomorphic sarcoma.

The biological behavior of ESOS varies with earlier series tend to indicate that they pursue aggressive local malignant disease and high rate of lung metastasis with patients succumbing to metastatic disease within 2-3 years after the initial diagnosis. Owing to this prior poor prognostic reputation and a 5-year survival rate of 25%, wide local excision including amputation to achieve negative margins has been considered as the best option. However, recent studies from the Cooperative Oncology Study Group in Germany and the Japanese Musculoskeletal Oncology Group indicated that the use of multimodal treatment including multiagent chemotherapy regimens and surgery (limb salvage or amputation) similar to those used in conventional OS can improve the prognosis Multiagent chemotherapy using API/AI sequential regimen, which combined adriamycin (A), cis-platinum (P), and ifosfamide (I), is currently preferred in many centres. Tumor size, histologic subtype, and proliferation index have been proposed as prognostic variables.

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Quiz 4

a. Infection (abscess or acute osteomyelitis), inflammatory-like condition (myositis ossificans) and primary malignant bone tumour (osteosarcoma). Imaging studies either plain radiographs or MRI scan exclude myositis ossificans and abscess.
b. With plain radiographs depicting a typical triad of a diaphyseal location of permeative lytic bone destruction with reactive periosteal lamination and Codman triangle, and a large soft tissue component, the diagnosis of Ewing sarcoma is more likely. However, the diaphyseal location of the lesion is also characteristic feature for other round-cell tumours that percolate bone particularly lymphoma and eosinophilic granuloma/Langerhans cell histiocytosis). Tissue biopsy is required to narrow down the diagnoses to a definitive diagnosis. At biopsy, the pathological tissue appears as whitish grey and soft in consistency. A diagnosis of Ewing sarcoma is most likely.
c. Treatment of Ewing sarcoma involves multimodal therapy following proper staging procedures: MRI scans and/or CT to define local extension or soft tissue component and degree of cortical destruction, chest CT to detect lung metastasis, bone scans to detect osseous metastasis and tissue biopsy. Modern treatment of Ewing sarcoma consists of neo-adjuvant pre-operative chemotherapy, followed by limb-salvage surgery or amputation and consolidation chemotherapy. Current chemotherapy protocols are based on ifosfamide and etoposide in addition to a combination of vincristine, dactinomycin, cyclophosphamide and doxorubicin (VACA). The final assessment of histological response to chemotherapy and the analysis of post-resection surgical margins are important determinants used to decide for adjuvant therapy. Amputation is now exclusively reserved for bulky tumour involving vital structures.

EWING SARCOMA (ES) AND EWING SARCOMA FAMILY OF TUMORS (ESFTs)

Evolving knowledge on the histogenesis of the tumor that was originally believed to be an endothelioma (Ewing,1921) has revealed that this poorly differentiated tumor belongs to a group of primitive round cell tumors collectively named as ESFTs (skeletal and extraskeletal Ewing sarcoma, primitive neuroectodermal tumor, neuroepithelioma and Askin tumor of the chest wall). This family of malignant bone and soft tissue tumors arises from pluripotent mesenchymal stem cell and shares common genotype, basal immonuphenotype and morphological features with variable phenotyphic neuroectodermal differentiation through specific chimeric transcripts. Classical ES represents the most primitive and primitive neuroectodermal tumor (PNET) is the most differentiated as regard to neuroectodermal differentiation.

ESFTs accounted for 6%-8% of primary malignant bone tumors, representing the third most frequent primary bone sarcoma after osteosarcomas and chondrosarcomas. ES per se account for approximately 10% of all primary bone tumors, second to osteosarcomas in-term of occurrence. PNET is relatively rare in bone, representing 10% of all ESFTs.

Clinical presentations of ESFTs vary with the majority of patients (80%) are adolescents or young adults below 20 years of age. They are rare before the age of 5 and after the age of 30. In children below 5 years of age, metastatic neuroblastoma should be conscientiously excluded. PNET tends to afflict patients with a broader age range. With exception for Askin tumor of the chest wall, ES/PNET have a slight male predomination with tendency to occur in the long bone or deep tissues of extremity. The typical presentation includes a rapidly growing painful palpable mass with associated systemic symptoms of fever, anaemia and weight loss suffice to masquerade as an acute osteomyelitis. Laboratory findings of leukocytosis and raised ESR may mislead to a diagnosis of acute osteomyelitis and catastrophically delay the treatment.

The vast majority of ES originate centrally in the diaphysis and metadiaphysis of a large long bone, or in a flat bone. Radiographically, an aggressive permeative/infiltrative lytic lesion with narrow transitional zone often without frank cortical destruction despite the presence of a large soft tissue mass/component (best seen on post-contrast MRI) indicates the tumour has tendency to infiltrate through small cortical perforations. Marrow involvement is best seen on MRI and skip lesions are picked up in less than 5% of patients. About 1% of ES appear sclerotic, due to reactive bone formation. Multilaminar periosteal reaction either parallel (onion peel) or perpendicular to the cortex (sun-burst), is sometimes prominent. Tumour involving flat bone is difficult to visualize on plain radiographs or CT images but readily visible as soft tissue mass on MRI. On imaging studies, the differential diagnoses should include acute osteomyelitis and lymphoma.

Grossly, the tumor may be glistening firm or soft and friable grey to white in color, mimicking pus. Haemorrhage and cystic necrotic changes may present.

The tumor cells typically appear as a tightly packed nodular growth of sheet-like cells in a compressed but minimal fibrovascular stroma or in large lobulated nests of uniformly undifferentiated/poorly differentiated small round to polygonal cells with indistinct scanty cytoplasm occasionally vacuolated by intracytoplasmic glycogen deposits, ovoid nuclei with indistinct nucleoli and distinct nuclear membrane. The chromatin shows fine granular pattern but mitotic figures vary> 20 mitoses per HPF. In many instances, broad zones of geographic necrosis are present as pseudoalveolar pattern with blood lakes (perivascular cuffing). There is no matrix production (osteoid or cartilage) by tumor cells.

An atypical ES often displays on of more of the features: lack of glycogen, brisk mitoses (over 2 per HPF), neoplastic vascular formation, spindling at the periphery of the tumor, some amount of ECM, lobular architecture or alveolar pattern. Variants of the classic pattern include large-cell type and a filigree pattern. Large-cell variant displays round cells with moderate nuclear enlargement, irregular nuclear contour and prominent nucleoli. The filigree pattern which shows bi-cellular architecture separated by stroma has a poorer outcome. Henamgiopericytomatous pattern of ES shows spindle-shaped neoplastic cells with thin-walled vessels.

At the other end of morphologic spectrum, PNETs show sheets or nodules of small round cells containing round or oval nuclei with scattered areas of such cells possessing abundant cytoplasm and elongated cytoplasmic processes which coalesce into rosettes resembling neuroblastoma. Most PNET rosettes have a central neurofibrillary core (Homer-Wright type). The tumor cells may form cords or small acinar-like nests reminiscent of a carcinoid tumour or small cell carcinoma.

Immunohistochemical molecular diagnostic techniques are of great help in establishing the diagnosis of ESFT. IHC staining for Mic2 (CD99) marking the protein of a pseudoautosomal gene located on the X- and Y-chromosome shows diffuse cytoplasmic membranous staining in 90% of cases (cytoplasmic staining is positive in some RMS and ALL). About 75% show positivity for nuclear staining with FLI-1 antibody. The more differentiated tumors (atypical ES and PNET) express NSE with negative Chromogranin A, CD56, synaptophysin, S-100 protein, vimentin and cytokeratin (adamantinoma-like ES).

Fluorescence in-situ hybridization (FISH), cytogenetics and reverse-transcriptase PCR techniques are useful to identify non-random reciprocal translocations of EWS gene with one of the members of ESFT transcription factors (FLI-1, ERG, ETV-1 and EIAF genes) on chromosome 11q24, 21q22, 7p22 or 17q12. These include t(11:22)(q24:q12) fusion of FLI-1 and ESW in 90%-95% of cases and t(21:22)(q22:q12) fusion of ERG and ESW in 5% to 10% of cases. Other gene fusion partners are rare occurrences in less than 1% of cases. Demonstartion of one of these specific translocations especially FLI-1 protein within the nuclei of small round cell tumors (85-90% of cases) is considered diagnostic of ES/PNET and is also included in ES therapeutic protocol for detection of residual disease and metastasis.

The staging of ESFT is based on the AJC on cancer/IUAC TNM classification parameters: tumor size (8cm being the cut-off), nodal involvement, metastases and Broder tumor grading.

Primary Tumor Extent (T)		**Regional Nodes (RN)**	
Tx	can't be evaluated	Nx	can't be evaluated
T0	no evidence of primary tumor	N0	no RN metastasis
T1	primary tumor longest axis <8cm in greatest dimension	N1	RNs metastasis
		Metastasis and Distant Node (M)	
T2	greatest dimension >8cm	Mx	can't be evaluated
T3	tumor discontinuation in the primary bone site	M0	no distant metastasis
		M1a	lung metastasis
		M1b	other distant metastasis

As ES is a high-grade malignant tumor, its stage grouping begins as stage II disease.

- Stage IIA T1, N0 or NX, M0
- Stage IIB T2, N0 or NX, M0
- Stage III T3, N0 or NX, M0
- Stage IVA any T, N0 or NX, M1a
- Stage IVB any T, N1, any M
  any T, any N, M1b

ES typically show aggressive course previously reputed to have poor and fatal outcome owing to high incidence of metastasis to the lung (20%), other bones (5%) and occult micrometastases (80%) even at time of presentation and diagnosis. Before the introduction of modern multiagent chemotherapy protocols, 90% of ES patients eventually died of the disease. However, with multimodal treatment: pre-operative neo-adjuvant chemotherapy, limb-sparing surgery or amputation, and adjuvant chemotherapy or radiation therapy, the outcome has changed to become a potentially curable disease with an expectable 5-YSR of 75% and 50% cure rate (PNET has a 10-YSR of 90% and long-term cure rate of <30% with metastasis). Standard 10-12 weeks of initial systemic induction chemotherapy with vincristine, cyclophosphamide, adriamycin, and dactomycin (VACA) is aimed at rapid initial cytoreduction to facilitate local control interventions: surgical ablation when feasible and radiotherapy if surgically inaccessible. The role of surgery has shifted from traditionally reserved for expendable bones (fibula, clavicle, scapula, rays of the hands and feet, and localized areas of the rib and pelvis to primary resection and reconstruction or prophylactic internal fixation after chemotherapy with or without radiation therapy. Growing evidence indicates that complete resection of the tumor appears capable of decreasing the risk for local recurrence. Radiation therapy continues to be a useful adjuvant for patients with post-resection residual disease or close surgical margins, surgically inaccessible tumor site, advanced disease and prophylactic pulmonary irradiation. In general, favorable prognostic factors in ES include:

- age below 17 years
- extremity involvement (distal>proximal)
- appendicular > axial tumor
- tumor < 8cm in greatest diameter
- no extension into soft tissue
- no soft tissue and non-metastatic disease
- type-1 EWS-FLI-1 fusion transcript
- >90% tumor necrosis after neo-adjuvant chemotherapy
- surgically excised diseased bone

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