Ontario Health
Cancer Care Ontario

Consensus Pathology Recommendations for Mesenchymal Tumours of Soft Tissue and Bone

March 2023

Table of Contents

Introduction

Sarcomas are malignant tumours of mesenchymal origin affecting individuals of all ages and occurring in ostensibly any part of the body. These rare neoplasms account for approximately 1% of adult cancers and 15% of pediatric cancers. According to the 2020 WHO Classification of Soft Tissue and Bone Tumours, there are approximately 200 different recognized histologic subtypes of soft tissue and bone tumours (International Agency for Research on Cancer [IARC], 2020). It is estimated that approximately 80% of all sarcomas arise in the soft tissue while about 20% occur in bone. In Canada, there were 1150 cases of Soft-tissue Sarcomas (STS) and 285 cases of bone cancers reported in 2018, and 160 cases of childhood bone cancers reported between 2012 and 2016. [1, 2, 3]

Sarcomas require complex care involving a multidisciplinary team that includes pathologists, radiologists, surgeons, radiation oncologists, medical oncologists, and medical geneticists, among others.[4] This multidisciplinary care is typically based at centres managing a high number of patients annually.[4]

In Ontario, Ontario Health (Cancer Care Ontario)'s (OH-CCO) Specialized Services Oversight program developed a "Provincial Sarcoma Services Plan" in 2015 aimed at providing equitable access to high-quality sarcoma services, optimizing care and services, and providing an overview of the funding of sarcoma services in the province.[4] Sarcoma services are organized through three multi-regional collaborative sarcoma programs. Within each program is a 'Host Site' which provides a full spectrum of specialized sarcoma services, as well as 'Partner Sites' that provide a sub-set of clinical services as part of their programs.[4] This document aims to expand on the existing Sarcoma Services plan and provide advice around pathology best practices for soft-tissue and bone sarcomas. This report also offers guidance on the tumours requiring referral to a Sarcoma Host Site as well as the tumours which may benefit from molecular investigations.

Due to the increasing diagnostic and therapeutic role of molecular findings in patient management decisions, a working group of pathologists with a special interest in sarcoma pathology along with medical oncologists specializing in sarcoma were asked to provide input to these recommendations.

Preamble

- The application of ancillary biomarker testing is increasingly important for the diagnosis and management of soft tissue and bone tumours. Biomarkers can be assessed by a variety of techniques including immunohistochemical and molecular assays.
- Technologies to identify biomarkers constantly evolve, and laboratory infrastructure can be variable. It is important that each laboratory adopt technologies and practices that reflect the scope of their predominant patient populations. It is the responsibility of the laboratory, in conjunction with established Communities of Practice, to ensure that minimum established biomarkers and parameters of test performance are met. This process is predicated upon rigorous in-house optimization and validation, application of appropriate controls in testing, and external proficiency testing, regardless of the methods or platforms chosen.
- A community of practice exists at sites diagnosing and treating soft tissue and bone tumours. This includes subspecialists, with access to the required biomarkers necessary for patient diagnosis and management.
- The investigation of hereditary disorders, and specific testing for hereditary causes of soft tissue and bone tumours is not included in these recommendations and has been identified as a topic for future consideration.
- The advice in this document, and the list of useful genomic biomarkers for the diagnosis of soft tissue and bone tumours, should be reviewed regularly, in line with future WHO Classification releases or as clinically necessary.

Mesenchymal Tumours of Soft Tissue and Bone

Classification

- Tumours should be classified per the 2020 World Health Organization Classification of Tumours of Soft Tissue and Bone[6] (Appendix A: Table 1, Table 2, Table 3)
- Histologic grade should be applied using the FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer) grading system[5] (Appendix A: Table 4)

Diagnostic Workup

- For all soft tissue and bone tumours:
    - All malignant soft tissue and bone tumours as well as a subset of tumours that are benign or of intermediate biologic potential should be referred to a Sarcoma Host Site
        - See Appendix B: Table 5 for a full list of indications requiring referral to a Sarcoma Host Site, other disease site groups, or paediatric sites
    - Any soft tissue or bone tumour in which there is diagnostic uncertainty or concern, or tumours which may fall outside of the recommendations in this document should be referred to a Sarcoma Host Site for evaluation
    - Cases potentially benefiting from specific genomic biomarkers for diagnostic sub-classification, prognosis, and/or therapeutic guidance should be referred to a Sarcoma Host Site where an expert in sarcoma pathology will pursue any testing warranted
    - Acknowledging differences in volume and practice requirements at each of the Sarcoma Host Sites, testing methodologies and test menus remain at the discretion of the respective sites. A summary of recommended genomic tests for Sarcoma Host Sites offering molecular analysis are given in Appendix B: Table 6. In order to maintain proficiency, some sites may elect to refer material out to other centres when rare tests are indicated. It is also important that laboratories remain responsive to new and emerging diagnostic and prognostic markers.

Turn-around times (TAT - in Calendar Days)

- Immunohistochemical evaluation – within 7 days
- Molecular evaluation – within 21 days

Topics requiring further investigation

- Data Requirements
- Incorporation of new/emerging mutations

Appendix A:

Table 1: WHO Classification of Soft Tissue Tumours[6]

Adipocytic Tumours	ICD - O Codes
Lipoma	
Lipoma NOS	8850/0
Lipomatosis	None
Lipomatosis of nerve	None
Lipoblastoma and lipoblastomatosis	
Lipoblastomatosis	8881/0
Angiolipoma	
Angiolipoma NOS	8861/0
Myolipoma of soft tissue	
Myolipoma	8890/0
Chondroid lipoma	8862/0
Spindle cell lipoma and pleomorphic lipoma	
Spindle cell lipoma	8857/0
Hibernoma	8880/0
Atypical spindle cell / pleomorphic lipomatous tumour	8857/0
Atypical lipomatous tumour / well-differentiated liposarcoma	
Atypical lipomatous tumour	8850/1
Liposarcoma, well-differentiated, NOS	8851/3
Dedifferentiated liposarcoma	8858/3
Myxoid liposarcoma	8852/3
Pleomorphic liposarcoma	8854/3
Myxoid pleiomorphic liposarcoma	8859/3

Fibroblastic and Myofibroblastic Tumours	ICD - O Codes
Nodular Fasciitis	8828/0
Proliferative fasciitis and proliferative myositis	
Proliferative fasciitis	8828/0
Proliferative myositis	8828/0
Myositis Ossificans and fibro-osseous pseudotumour of digits	None
Ischaemic Fasciitis	None
Elastofibroma	8820/0
Fibrous hamartoma of infancy	8992/0
Fibromatosis colli	None
Juvenile hyaline fibromatosis	None
Inclusion body fibromatosis	None
Fibroma of tendon sheath	8813/0
Desmoplastic fibroblastoma	8810/0
Myofibroblastoma	8825/0
Calcifying aponeurotic fibroma	8816/0
EWSR-SMAD3-positive fibroblastic tumour (emerging)	None
Angiomyofibroblastoma	8826/0
Cellular angiofibroma	9160/0
Angiofibroma of soft tissue	
Angiofibroma	9160/0
Nuchal-type fibroma	
Nuchal fibroma	8810/0
Acral fibromyxoma	8811/0

Fibroblastic and Myofibroblastic Tumours	ICD - O Codes
Gardner Fibroma	8810/0
Palmar fibromatosis and plantar fibromatosis	
Palmar/plantar-type fibromatosis	8813/1
Desmoid fibromatosis	
Desmoid-type fibromatosis	8821/1
Lipofibromatosis	8851/1
Giant cell fibroblastoma	8834/1
Dermatofibrosarcoma protuberans	
Dermatofibrosarcoma protuberans NOS	8832/1
Solitary fibrous tumour	
Solitary fibrous tumour, benign	8815/0
Solitary fibrous tumour, NOS	8815/1
Solitary fibrous tumour, malignant	8815/3
Inflammatory myofibroblastic tumour	8825/1
Low-grade Myofibroblastic sarcoma	
Myofibroblastic sarcoma	8825/3
Superficial CD34-positive fibroblastic tumour	8810/1
Myxoinflammatory fibroblastic sarcoma	8811/1
Infantile fibrosarcoma	8814/3
Solitary fibrous tumour, malignant	8815/3
Adult Fibrosarcoma	
Fibrosarcoma NOS	8810/3
Myxofibrosarcoma	8811/3
Low-grade fibromyxoid sarcoma	8840/3
Sclerosing epithelioid fibrosarcoma	8840/3

So-Called Fibrohystiocytic Tumours	ICD - O Codes
Tenosynovial Giant cell tumour	
Tenosynovial Giant cell tumour NOS	9252/0
Deep fibrous histiocytoma	
Deep benign fibrous histiocytoma	8831/0
Plexiform fibrohistiocytic tumour	8835/1
Giant cell tumour of soft tissue	
Giant cell tumour of soft parts	9251/1

Vascular Tumours	ICD - O Codes
Synovial haemangioma	9120/0
Haemangioma NOS	
Intramuscular haemangioma	9132/0
Arteriovenous malformation/haemangioma	9123/0
Venous haemangioma	9122/0
Anastomising haemangioma	
Haemangioma NOS	9120/0
Epithelioid haemangioma	9125/0
Lymphangioma and lymphangiomatosis	
Lymphangioma NOS	9170/0
Lymphangiomatosis	9173/0

Vascular Tumours	ICD - O Codes
Tufted angioma and kaposiform haemangioendothelioma	
Acquired Tufted haemangioma	9161/0
Kaposiform haemangioendothelioma	9130/1
Retiform haemangioendothelioma	9136/1
Papillary intralymphatic angioendothelioma	9135/1
Composite haemangioendothelioma	9136/1
Kaposi sarcoma	9140/3
Pseudomyogenic haemangioendothelioma	
Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma	9138/1
Epithelioid haemangioendothelioma	
Epithelioid haemangioendothelioma NOS	9133/3
Angiosarcoma	9120/3
Pericytic (Perivascular) tumours	
Glomus tumour	
Glomus tumour, NOS	8711/0
Myopericytoma, including myofibroma	
Myopericytoma	8824/0
Angioleiomyoma	8894/0

Smooth Muscle Tumours	ICD - O Codes
Leiomyoma	
Leiomyoma, NOS	8890/0
EBV-associated smooth muscle tumour	
Smooth muscle tumour of uncertain malignant potential	8897/1
Inflammatory leiomyosarcoma	
Leiomyosarcoma NOS	8890/3
Leiomyosarcoma	
Leiomyosarcoma NOS	8890/3

Skeletal Muscle Tumours	ICD - O Codes
Rhabdomyoma	
Rhabdomyoma NOS	8900/0
Embryonal rhabdomyosarcoma	
Embryonal rhabdomyosarcoma NOS	8910/3
Alveolar rhabdomyosarcoma	8920/3
Pleomorphic rhabdomyosarcoma	
Pleomorphic rhabdomyosarcoma NOS	8901/3
Spindle cell / sclerosing rhabdomyosarcoma	
Spindle cell rhabdomyosarcoma	8912/3
Ectomesenchymoma	8921/3

Gastrointestinal Stromal Tumours	ICD - O Codes
Gastrointestinal stromal tumour	8936/3

Chondro-Osseous Tumours	ICD - O Codes
Soft tissue chondroma	
Chondroma NOS	9220/0
Extraskeletal osteosarcoma	
Osteosarcoma, extraskeletal	9180/3

Peripheral Nerve Sheath Tumours	ICD - O Codes
Schwannoma	
Schwannoma NOS	9560/0
Neurofibroma	
Neurofibroma NOS	9540/0
Perineurioma	
Perineurioma NOS	9571/0
Granular cell tumour	
Granular cell tumour NOS	9580/0
Nerve sheath myxoma	9562/0
Solitary circumscribed neuroma	9570/0
Ectopic Meningioma and meningiothelial hamartoma	
Meningioma NOS	9530/0
Benign Triton tumour / neuromuscular choristoma	None
Hybrid nerve sheath tumour	9563/0
Malignant peripheral nerve sheath tumour	
Malignant peripheral nerve sheath tumour NOS	9540/3
Malignant melanotic nerve sheath tumour	9540/3

Tumours of Uncertain Differentiation	ICD - O Codes
Intramuscular myxoma	
Myxoma NOS	8840/0
Juxta-articular myxoma	
Myxoma NOS	8840/0
Deep (aggressive) angiomyxoma	
Aggressive angiomyxoma	8841/0
Atypical fibroxanthoma	8830/1
Angiomatoid fibrous histiocytoma	8836/1
Ossifying fibromyxoid tumour	
Ossifying fibromyxoid tumour NOS	8842/0
Myoepithelioma, myoepithelial carcinoma, and mixed tumour	
Myoepithelioma NOS	8982/0
Mixed tumour NOS	8940/0
Pleomorphic hyalinizing angiectatic tumour of soft parts	
Pleomorphic hyalinizing angiectatic tumour	8802/1
Haemosiderotic fibrolipomatous tumour	8811/1
Phosphaturic mesenchymal tumour	
Phosphaturic mesenchymal tumour NOS	8990/0
NTRK-rearranged spindle cell neoplasm (emerging)	None
Synovial Sarcoma	
Synovial sarcoma NOS	9040/3
Epithelioid Sarcoma	8804/3
Alveolar soft part sarcoma	9581/3
Clear cell sarcoma of soft tissue	
Clear cell sarcoma NOS	9044/3
Extraskeletal myxoid chondrosarcoma	9231/3
Desmoplastic small round cell tumour	8806/3

Tumours of Uncertain Differentiation	ICD - O Codes
Extrarenal Rhabdoid tumour Rhabdoid tumour NOS	8963/3
PEComa Perivascular epithelioid tumour, benign	8714/0

Tumours of Uncertain Differentiation	ICD - O Codes
Intimal sarcoma	9137/3
Undifferentiated sarcoma	8805/3

Table 2: WHO Classification of Undifferentiated Small Round Cell Sarcomas of Bone and Soft Tissue [6]

Undifferentiated Small Round Cell Sarcomas of Bone and Soft Tissue	ICD - O Codes
Ewing Sarcoma	9364/3
Round cell sarcoma with *EWSR1*-non-ETS fusions	9366/3
CIC-rearranged sarcoma	9367/3
Sarcoma with *BCOR* genetic alterations	9368/3

Table 3: WHO Classification of Tumours of Bone [6]

Chondrogenic Tumours	ICD - O Codes
Subungual exostosis	9213/0
Bizarre parosteal osteochonromatous proliferation	9212/0
Periosteal chondroma	9221/0
Enchondroma	9220/0
Osteochondroma	9210/0
Chondroblastoma Chondroblastoma NOS	9230/0
Chondromyxoid fibroma	9241/0
Osteochondromyxoma	9211/0
Synovial chondromatosis	9220/1
Central atypical cartilaginous tumour / chondrosarcoma, grade 1 Atypical cartilaginous tumour Chondrosarcoma, grade 1	 9222/1 9222/3
Secondary peripheral atypical cartilaginous tumour / chondrosarcoma, grade 1 Atypical cartilaginous tumour Chondrosarcoma, grade 1	 9222/1 9222/3
Central Chondrosarcoma, grade 2 and 3 Chondrosarcoma, grade 2 Chondrosarcoma, grade 3	 9220/3 9220/3
Secondary peripheral chondrosarcoma, grade 2 and 3 Chondrosarcoma, grade 2 Chondrosarcoma, grade 3	 9220/3 9220/3
Periosteal chondrosarcoma	9221/3
Clear cell chondrosarcoma	9242/3
Mesenchymal chondrosarcoma	9240/3
Dedifferentiated chondrosarcoma	9243/3

Osteogenic Tumours	ICD - O Codes
Osteoma	9180/0
Osteoid Osteoma	9191/0

Osteogenic Tumours	ICD - O Codes
Osteoblastoma Osteoblastoma NOS	 9200/1
Low-grade central osteosarcoma	9187/3
Osteosarcoma Osteosarcoma NOS	 9180/3
Parosteal osteosarcoma	9192/3
Periosteal osteosarcoma	9193/3
High-grade surface osteosarcoma	9194/3
Secondary osteosarcoma	9184/3

Fibrogenic Tumours	ICD - O Codes
Desmoplastic fibroma of bone Desmoplastic fibroma	 8823/1
Fibrosarcoma of bone Fibrosarcoma NOS	 8810/3

Vascular Tumours of Bone	ICD - O Codes
Haemangioma of bone Haemangioma NOS	 9120/0
Epithelioid haemangioma of bone Epithelioid haemangioma	 9125/0
Epithelioid haemangioendothelioma of bone Epithelioid haemangioendothelioma NOS	 9133/3
Angiosarcoma of bone Angiosarcoma	 9120/3

Osteoclastic Giant Cell Rich Tumours	ICD - O Codes
Aneurysmal bone cyst	9260/0
Giant cell tumour of bone	9250/1
Non-ossifying fibroma	8830/0

Notochordal Tumours	ICD - O Codes
Benign notochordal cell tumour	9370/0
Conventional chordoma	9370/3

Notochordal Tumours	ICD - O Codes
Dedifferentiated chordoma	9372/3
Poorly differentiated chordoma	9370/3

Other Mesenchymal Tumours of Bone	ICD - O Codes
Chondromesenchymal hamartoma of chest wall	None
Osteofibrous dysplasia	None
Adamantinoma of long bones Osteofibrous dysplasia–like adamantinoma Adamantinoma of long bones	 9261/1 9261/3
Simple bone cyst	None
Fibrocartilaginous mesenchymoma	8890/1
Fibrous dysplasia	8818/0
Lipoma and hibernoma of bone Lipoma NOS Hibernoma	 8850/0 8880/0
Leiomyosarcoma of bone Leiomyosarcoma NOS	 8890/3
Osteofibrous dysplasia-like adamantinoma	8261/1
Undifferentiated Pleomorphic sarcoma Pleomorphic sarcoma, undifferentiated	 8802/3

Other Mesenchymal Tumours of Bone	ICD - O Codes
Bone Metastases	None

Haematopoietic Neoplasms of bone	ICD - O Codes
Solitary Plasmacytoma of bone Plasmacytoma of bone	 9731/3
Primary non-Hodgkin lymphoma of bone Malignant lymphoma, non-Hodgkin, NOS Hodgkin disease NOS Diffuse large B-cell lymphoma NOS Follicular lymphoma NOS Marginal zone B-cell lymphoma NOS T-cell lymphoma NOS Anaplastic large cell lymphoma NOS Malignant lymphoma, lymphoblastic, NOS Burkitt lymphoma NOS	 9591/3 9650/3 9680/3 9690/3 9699/3 9702/3 9714/3 9727/3 9687/3
Langerhans cell histiocytosis Langerhans cell histiocytosis NOS Langerhans cell histiocytosis, disseminated	 9751/1 9751/3
Erdheim-Chester disease	9749/3
Rosai-Dorfman disease	None

Table 4: FNCLCC (Fédération Nationale de Centres de Lutte Contre le Cancer) Grading System (adapted from Coindre JM, 2006)[5]

Histological Parameter	Definition
Tumour differentiation	• Score 1: Sarcomas closely resembling normal adult mesenchymal tissue and potentially difficult to distinguish from the counterpart benign tumour (e.g., well-differentiated liposarcoma, well-differentiated leiomyosarcoma) • Score 2: Sarcomas for which histological typing is certain (e.g., myxoid liposarcoma, myxofibrosarcoma) • Score 3: Embryonal and undifferentiated sarcomas, synovial sarcomas, sarcomas of doubtful type
Mitotic count (established on the basis of 10 HPF; 1HPF measures 0.1734mm^2)	• Score 1: 0-9 mitoses per 10 HPF * • Score 2: 10-19 mitoses per 10 HPF * • Score 3: > 19 mitoses per 10 HPF *
Tumour necrosis	• Score 0: no necrosis • Score 1: < 50% tumour necrosis • Score 2: ≥ 50% tumour necrosis
Histological grade	• Grade 1: total score 2, 3 • Grade 2: total score 4, 5 • Grade 3: total score 6, 7, 8

* HPF – high-power field

Appendix B:

Table 5: Tumours Requiring Referral to a Sarcoma Host Site or Disease Site Group (adapted from IARC, 2020)[6]

All malignant soft tissue and bone tumours, and select benign and intermediate tumours should be referred to a Sarcoma Host Site, or appropriate disease site group.

WHO CLASSIFICATION OF TUMOURS OF SOFT TISSUE

Tumour Classification	WHO - Tumour Name	ICD - O Codes	Biologic Potential
Adipocytic Tumours	Dedifferentiated liposarcoma	8858/3	Malignant
Adipocytic Tumours	Myxoid liposarcoma	8852/3	Malignant
Adipocytic Tumours	Pleomorphic liposarcoma	8854/3	Malignant
Adipocytic Tumours	Myxoid pleiomorphic liposarcoma	8859/3	Malignant
Fibroblastic and Myofibroblastic Tumours	Solitary fibrous tumour Solitary fibrous tumour, benign Solitary fibrous tumour, NOS Solitary fibrous tumour, malignant	 8815/0 8815/1 8815/3	Intermediate (rarely metastasizing)
Fibroblastic and Myofibroblastic Tumours	Inflammatory myofibroblastic tumour	8825/1	Intermediate (rarely metastasizing)
Fibroblastic and Myofibroblastic Tumours	Low-grade Myofibroblastic sarcoma Myofibroblastic sarcoma	 8825/3	Intermediate (rarely metastasizing)
Fibroblastic and Myofibroblastic Tumours	Superficial CD34-positive fibroblastic tumour	8810/1	Intermediate (rarely metastasizing)
Fibroblastic and Myofibroblastic Tumours	Myxoinflammatory fibroblastic sarcoma	8811/1	Intermediate (rarely metastasizing)
Fibroblastic and Myofibroblastic Tumours	Infantile fibrosarcoma	8814/3	Intermediate (rarely metastasizing)
Fibroblastic and Myofibroblastic Tumours	Solitary fibrous tumour, malignant	8815/3	Malignant
Fibroblastic and Myofibroblastic Tumours	Adult Fibrosarcoma Fibrosarcoma NOS	 8810/3	Malignant
Fibroblastic and Myofibroblastic Tumours	Myxofibrosarcoma	8811/3	Malignant
Fibroblastic and Myofibroblastic Tumours	Low-grade fibromyxoid sarcoma	8840/3	Malignant
Fibroblastic and Myofibroblastic Tumours	Sclerosing epithelioid fibrosarcoma	8840/3	Malignant
So-Called Fibrohystiocytic Tumours	Giant cell tumour of soft tissue Giant cell tumour of soft parts	 9251/1	Intermediate (rarely metastasizing)
Vascular Tumours	Tufted angioma and kaposiform haemangioendothelioma Acquired Tufted haemangioma Kaposiform haemangioendothelioma	 9161/0 9130/1	Benign
Vascular Tumours	Retiform haemangioendothelioma	9136/1	Intermediate (rarely metastasizing)

Tumour Classification	WHO - Tumour Name	ICD - O Codes	Biologic Potential
Vascular Tumours	Papillary intralymphatic angioendothelioma	9135/1	Intermediate (rarely metastasizing)
Vascular Tumours	Composite haemangioendothelioma	9136/1	Intermediate (rarely metastasizing)
Vascular Tumours	Kaposi sarcoma	9140/3	Intermediate (rarely metastasizing)
Vascular Tumours	Pseudomyogenic haemangioendothelioma Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma	9138/1	Intermediate (rarely metastasizing)
Vascular Tumours	Epithelioid haemangioendothelioma Epithelioid haemangioendothelioma NOS	9133/3	Malignant
Vascular Tumours	Angiosarcoma	9120/3	Malignant
Smooth Muscle Tumours	EBV-associated smooth muscle tumour Smooth muscle tumour of uncertain malignant potential	8897/1	Benign and Intermediate
Smooth Muscle Tumours	Inflammatory leiomyosarcoma Leiomyosarcoma NOS	8890/3	Malignant
Smooth Muscle Tumours	Leiomyosarcoma Leiomyosarcoma NOS	8890/3	Malignant
Skeletal Muscle Tumours	Rhabdomyoma Rhabdomyoma NOS	8900/0	Benign
Skeletal Muscle Tumours	Embryonal rhabdomyosarcoma Embryonal rhabdomyosarcoma NOS	8910/3	Malignant
Skeletal Muscle Tumours	Alveolar rhabdomyosarcoma	8920/3	Malignant
Skeletal Muscle Tumours	Pleomorphic rhabdomyosarcoma Pleomorphic rhabdomyosarcoma NOS	8901/3	Malignant
Skeletal Muscle Tumours	Spindle cell / sclerosing rhabdomyosarcoma Spindle cell rhabdomyosarcoma	8912/3	Malignant
Skeletal Muscle Tumours	Ectomesenchymoma	8921/3	Malignant
Gastrointestinal Stromal Tumours	Gastrointestinal stromal tumour	8936/3	Malignant
Chondro-Osseous Tumours	Extraskeletal osteosarcoma Osteosarcoma, extraskeletal	9180/3	Malignant
Peripheral Nerve Sheath Tumours	Malignant peripheral nerve sheath tumour Malignant peripheral nerve sheath tumour NOS	9540/3	Malignant
Peripheral Nerve Sheath Tumours	Malignant melanotic nerve sheath tumour	9540/3	Malignant
Tumours of Uncertain Differentiation	Atypical fibroxanthoma	8830/1	Intermediate (rarely metastasizing)
Tumours of Uncertain Differentiation	Angiomatoid fibrous histiocytoma	8836/1	Intermediate (rarely metastasizing)

Tumour Classification	WHO - Tumour Name	ICD - O Codes	Biologic Potential
Tumours of Uncertain Differentiation	Ossifying fibromyxoid tumour Ossifying fibromyxoid tumour NOS	 8842/0	Intermediate (rarely metastasizing)
Tumours of Uncertain Differentiation	Myoepithelioma, myoepithelial carcinoma, and mixed tumour Myoepithelioma NOS Mixed tumour NOS	 8982/0 8940/0	Intermediate (rarely metastasizing)
Tumours of Uncertain Differentiation	Pleomorphic hyalinizing angiectatic tumour of soft parts Pleomorphic hyalinizing angiectatic tumour	 8802/1	Benign
Tumours of Uncertain Differentiation	Haemosiderotic fibrolipomatous tumour	8811/1	Intermediate (locally aggressive)
Tumours of Uncertain Differentiation	Phosphaturic mesenchymal tumour Phosphaturic mesenchymal tumour NOS	 8990/0	Benign
Tumours of Uncertain Differentiation	NTRK-rearranged spindle cell neoplasm (emerging)	None	Malignant
Tumours of Uncertain Differentiation	Synovial Sarcoma Synovial sarcoma NOS	 9040/3	Malignant
Tumours of Uncertain Differentiation	Epithelioid Sarcoma	8804/3	Malignant
Tumours of Uncertain Differentiation	Alveolar soft part sarcoma	9581/3	Malignant
Tumours of Uncertain Differentiation	Clear cell sarcoma of soft tissue Clear cell sarcoma NOS	 9044/3	Malignant
Tumours of Uncertain Differentiation	Extraskeletal myxoid chondrosarcoma	9231/3	Malignant
Tumours of Uncertain Differentiation	Desmoplastic small round cell tumour	8806/3	Malignant
Tumours of Uncertain Differentiation	Extrarenal Rhabdoid tumour Rhabdoid tumour NOS	 8963/3	Malignant
Tumours of Uncertain Differentiation	PEComa Perivascular epithelioid tumour, benign	 8714/0	Benign
Tumours of Uncertain Differentiation	Intimal sarcoma	9137/3	Malignant
Tumours of Uncertain Differentiation	Undifferentiated sarcoma	8805/3	Malignant

WHO CLASSIFICATION OF UNDIFFERENTIATED SMALL ROUND CELL SARCOMAS OF BONE AND SOFT TISSUE

Tumour Classification	WHO - Tumour Name	ICD - O Codes	Biologic Potential
Undifferentiated small round cell sarcomas of bone and soft tissue	Ewing Sarcoma	9364/3	Malignant

Tumour Classification	WHO - Tumour Name	ICD - O Codes	Biologic Potential
Undifferentiated small round cell sarcomas of bone and soft tissue	Round cell sarcoma with EWSR1-non-ETS fusions	9366/3	Malignant
Undifferentiated small round cell sarcomas of bone and soft tissue	CIC-rearranged sarcoma	9367/3	Malignant
Undifferentiated small round cell sarcomas of bone and soft tissue	Sarcoma with BCOR genetic alterations	9368/3	Malignant

WHO CLASSIFICATION OF TUMOURS OF BONE

Tumour Classification	WHO - Tumour Name	ICD - O Codes	Biologic Potential
Chondrogenic Tumours	Chondroblastoma Chondroblastoma NOS	 9230/0	Benign
Chondrogenic Tumours	Chondromyxoid fibroma	9241/0	Benign
Chondrogenic Tumours	Central atypical cartilaginous tumour / chondrosarcoma, grade 1 Atypical cartilaginous tumour Chondrosarcoma, grade 1	 9222/1 9222/3	Intermediate (locally aggressive)
Chondrogenic Tumours	Secondary peripheral atypical cartilaginous tumour / chondrosarcoma, grade 1 Atypical cartilaginous tumour Chondrosarcoma, grade 1	 9222/1 9222/3	Intermediate (locally aggressive)
Chondrogenic Tumours	Central Chondrosarcoma, grade 2 and 3 Chondrosarcoma, grade 2 Chondrosarcoma, grade 3	 9220/3 9220/3	Malignant
Chondrogenic Tumours	Secondary peripheral chondrosarcoma, grade 2 and 3 Chondrosarcoma, grade 2 Chondrosarcoma, grade 3	 9220/3 9220/3	Malignant
Chondrogenic Tumours	Periosteal chondrosarcoma	9221/3	Malignant
Chondrogenic Tumours	Clear cell chondrosarcoma	9242/3	Malignant
Chondrogenic Tumours	Mesenchymal chondrosarcoma	9240/3	Malignant
Chondrogenic Tumours	Dedifferentiated chondrosarcoma	9243/3	Malignant
Osteogenic Tumours	Low-grade central osteosarcoma	9187/3	Malignant
Osteogenic Tumours	Osteosarcoma Osteosarcoma NOS	 9180/3	Malignant
Osteogenic Tumours	Parosteal osteosarcoma	9192/3	Malignant
Osteogenic Tumours	Periosteal osteosarcoma	9193/3	Malignant
Osteogenic Tumours	High-grade surface osteosarcoma	9194/3	Malignant
Osteogenic Tumours	Secondary osteosarcoma	9184/3	Malignant
Fibrogenic Tumours	Fibrosarcoma of bone Fibrosarcoma NOS	 8810/3	Malignant

Tumour Classification	WHO - Tumour Name	ICD - O Codes	Biologic Potential
Osteoclastic Giant Cell Rich Tumours	Giant cell tumour of bone	9250/1	Intermediate (locally aggressive, rarely metastasizing)
Notochordal Tumours	Benign notochordal cell tumour	9370/0	Benign
Notochordal Tumours	Conventional chordoma	9370/3	Malignant
Notochordal Tumours	Dedifferentiated chordoma	9372/3	Malignant
Notochordal Tumours	Poorly differentiated chordoma	9370/3	Malignant
Other mesenchymal tumours of bone	Adamantinoma of long bones Osteofibrous dysplasia–like adamantinoma Adamantinoma of long bones	 9261/1 9261/3	Malignant
Other mesenchymal tumours of bone	Fibrocartilaginous mesenchymoma	8890/1	Intermediate (locally aggressive)
Other mesenchymal tumours of bone	Leiomyosarcoma of bone Leiomyosarcoma NOS	 8890/3	Malignant
Other mesenchymal tumours of bone	Osteofibrous dysplasia-like adamantinoma	8261/1	Intermediate (locally aggressive)
Other mesenchymal tumours of bone	Undifferentiated Pleomorphic sarcoma Pleomorphic sarcoma, undifferentiated	 8802/3	Malignant
Other mesenchymal tumours of bone	Bone Metastases	None	Malignant
Haematopoietic Neoplasms of bone	Solitary Plasmacytoma of bone Plasmacytoma of bone	 9731/3	Malignant
Haematopoietic Neoplasms of bone	Primary non-Hodgkin lymphoma of bone Malignant lymphoma, non-Hodgkin, NOS Hodgkin disease NOS Diffuse large B-cell lymphoma NOS Follicular lymphoma NOS Marginal zone B-cell lymphoma NOS T-cell lymphoma NOS Anaplastic large cell lymphoma NOS Malignant lymphoma, lymphoblastic, NOS Burkitt lymphoma NOS	 9591/3 9650/3 9680/3 9690/3 9699/3 9702/3 9714/3 9727/3 9687/3	Malignant
Haematopoietic Neoplasms of bone	Langerhans cell histiocytosis Langerhans cell histiocytosis NOS Langerhans cell histiocytosis, disseminated	 9751/1 9751/3	Intermediate (locally aggressive)
Haematopoietic Neoplasms of bone	Erdheim-Chester disease	9749/3	Intermediate (locally aggressive)
Haematopoietic Neoplasms of bone	Rosai-Dorfman disease	None	Benign

Table 6: Gene List for Molecular Analysis of Soft Tissue and Bone Tumours

- Sites performing molecular testing should have the capability to detect relevant genetic events (including SNV, fusion, amplification etc.)
- For gene fusions, the identification of both gene partners is preferable (i.e., NGS platforms, rather than FISH)
- New fusion partners are continuously being discovered. This list is anticipated to expand as the literature evolves.

Gene List for Molecular Analysis of Soft Tissue and Bone Tumours

ABL1	*ACTB*	*ACTL6A*	*ACVR2A*	*ADGRF5*	*AFF2*
AHRR	*ALK*	*APC*	*ARAF*	*ASPSCR1*	*ATF1*
BCOR	*BCORL1*	*BRAF*	*BRD4*	*CAMTA1*	*CCNB3*
CDK4	*CDKN2A*	*CDKN2B*	*CDX1*	*CDX2*	*CIC*
CHD7	*CHD9*	*CITED2*	*COL1A1*	*COL6A3*	*CREB1*
CREB3L1	*CREB3L2*	*CREB3L3*	*CREM*	*CSF1*	*CTNNB1*
DCTN1	*DDIT3*	*DUX4*	*EGFR*	*EMILIN2*	*EML4*
EPC1	*EP300*	*ERG*	*ETV1*	*ETV4*	*ETV6*
EWSR1	*EXT1*	*EXT2*	*FGF1*	*FGFR1*	*FGFR2*
FLI1	*FN1*	*FOS*	*FOSB*	*FOXO1*	*FUS*
GLI1	*GNAS*	*GREB1*	*H3-3A*	*H3-3B*	*HEY1*
HMGA2	*HRAS*	*IDH1*	*IDH2*	*IRF2BP2*	*JAZF1*
KHDRBS1	*KIT*	*KLF15*	*KMT2A*	*KRAS*	*LEUTX*
LMNA	*LPP*	*MAML2*	*MAMLD1*	*MALAT1*	*MAP2K1*
MAP3K1	*MBTD1*	*MDM2*	*MEAF6*	*MEIS1*	*MGEA5*
MN1	*MRTFB*	*MSN*	*MYC*	*MYOD1*	*NAB2*
NACC1	*NCOA1*	*NCOA2*	*NCOA3*	*NCOR2*	*NEDD4*
NF1	*NF2*	*NFATC1*	*NFATC2*	*NOTCH1*	*NOTCH2*
NR4A3	*NRAS*	*NTRK1*	*NTRK2*	*NTRK3*	*NUTM1*
NUTM2A	*NUTM2B*	*OGA*	*PATZ1*	*PAX*	*PBX1*
PAX7	*PBX3*	*PDGFB*	*PDGFD*	*PDGFRA*	*PDGFRB*
PHF1	*PIK3CA*	*PLAG1*	*POU2AF3*	*POU5F1*	*PRDM10*
PRKAR1A	*PRRX1*	*RAF1*	*RB1*	*RECQL4*	*RELA*
RET	*ROS1*	*RREB1*	*RTL9*	*SDHA*	*SDHB*
SERPINA7	*SMAD3*	*SMARCA2*	*SMARCA4*	*SMARCB1*	*SPECC1L*
SP3	*SRF*	*SQSTM1*	*SS18*	*SS18L1*	*SSX1*
SSX2	*SSX4*	*STAT6*	*SUZ12*	*TFCP2*	*TFE3*
TGFBR3	*THBS1*	*TAF15*	*TAF2N*	*TCF12*	*TP53*
TRAF7	*TSC1*	*TSC2*	*USP6*	*VCL*	*VGLL2*
VGLL3	*WT1*	*WWTR1*	*YAP1*	*YWHAE*	*ZC3H7B*
ZFTA	*ZNF444*				

References

1. Canadian Cancer Society. (n.d.). Childhood bone cancer statistics - Canadian Cancer Society. Retrieved March 8, 2019, from http://www.cancer.ca/en/cancer-information/cancer-type/bone-childhood/statistics/?region=on

2. Canadian Cancer Society. (n.d.). Bone cancer statistics - Canadian Cancer Society. Retrieved July 15, 2021, from http://www.cancer.ca/en/cancer-information/cancer-type/bone/statistics/?region=on

3. Canadian Cancer Society. (n.d.). Soft tissue sarcoma statistics - Canadian Cancer Society. Retrieved July 15, 2021, from http://www.cancer.ca/en/cancer-information/cancer-type/soft-tissue-sarcoma/statistics/?region=on

4. Ontario Health (Cancer Care Ontario). (2015). Provincial Sarcoma Services Plan. Retrieved from https://www.cancercareontario.ca/en/content/provincial-sarcoma-services-plan

5. Coindre J. M. (2006). Grading of soft tissue sarcomas: review and update. Archives of pathology & laboratory medicine, 130(10), 1448–1453. https://doi.org/10.5858/2006-130-1448-GOSTSR

6. International Agency for Research on Cancer (IARC). (2020). Soft Tissue and Bone Tumours (5th ed)/ WHO classification of tumours of soft tissue and bone. Retrieved May 11, 2021, from https://tumourclassification.iarc.who.int/paragraphcontent/33/279