Cancer Council Queensland

Australian Government
Cancer Australia

Childhood cancer staging for population registries

according to the

Toronto Childhood Cancer Stage Guidelines[1, 2]

Version 2

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Abbreviations

Abbreviation	
AJCC	American Joint Committee on Cancer
APCR	Australian Paediatric Cancer Registry
COG	Children's Oncology Group
CNS	Central nervous system
CSF	Cerebrospinal fluid
FIGO	International Federation of Gynaecological Oncologists
ICCC-3	International Classification of Childhood Cancer, Third Edition
ICD-O-3	International Classification of Diseases for Oncology – Third Edition
IDRF	Image-defined risk factors
INRGSS	International Neuroblastoma Risk Group Staging System
IRSS	International Retinoblastoma Staging System
M	Medulloblastoma
MIBG	Iodine-123 metaiodobenzylguanidine
MRI	Magnetic resonance imaging
MS	Metastatic special
MYCN	v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog
NOS	Not otherwise specified
NWTSG	National Wilms tumour Study Group
PNET	Primitive neuroectodermal tumour
pPNET	Peripheral neuroectodermal tumour
RBC	Red blood cell count
RMS	Rhabdomyosarcoma
SEER	Surveillance, Epidemiology and End Results Programme
SIOP	International Society of Paediatric Oncology
STaR	Staging, Treatment and Recurrence project
TNM	Tumour, lymph nodes, metastasis
UICC	Union for International Cancer Control
WBC	White blood cell count
WHO	World Health Organisation

Introduction

The collection of internationally consistent information on childhood cancer stage by population-based cancer registries is essential for epidemiologic analysis, international benchmarking and comparisons of childhood cancer incidence and outcomes.

The *Toronto Paediatric Cancer Stage Guidelines* for population cancer registries

A consensus meeting was convened in 2014 by the Union for International Cancer Control (UICC), the Dana-Farber Cancer Institute and the Hospital for Sick Children, Toronto to address the lack of consistent information on childhood cancer stage in population registries.[1] For each of a subset of the major childhood cancer diagnostic groups/subgroups, the meeting reviewed all disease-specific cancer staging systems currently in use and recommended the one most suitable for use by population-based cancer registries. The recommended staging systems are listed as the *Toronto Paediatric Cancer Stage Guidelines*.[1]

The *Guidelines* recommended disease-specific staging systems for acute lymphoblastic leukaemia, acute myeloid leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, Wilms tumour, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, osteosarcoma, Ewing sarcoma, retinoblastoma, hepatoblastoma, germ cell tumours (testicular cancer and ovarian cancer), medulloblastoma and ependymoma.

The *Guidelines* were successfully tested in practice for their feasibility and validity.[3] They are endorsed by the UICC TNM Prognostic Factors project, the European Network of Cancer Registries (ENCR), the Group for Cancer Epidemiology and Registration in Latin Language Countries (GRELL) and the African Network of Cancer Registries (ANCR) and published in the UICC TNM Classification of Malignant Tumours 8th Edition.[4]

The expert group was reconvened in Lyon in 2019. At this meeting, the Toronto Guidelines were reviewed and updated by consensus.[2] The main changes were that:

- a staging system was no longer considered appropriate for acute myeloid leukaemia;
- all renal tumours, with the exception of renal cell carcinomas, should use the endorsed staging systems for Wilms tumour;
- staging systems for osteosarcoma and Ewing sarcoma were combined into a single recommendation for all bone tumours;
- a staging system was endorsed for astrocytomas;
- the S category (serum tumour markers) was confirmed as an integral part of TNM staging for testicular cancer in Tier 2 recommendations; and
- PRETEXT number was added to Tier 2 recommendations for hepatoblastoma.

This manual provides detailed descriptions of the staging systems recommended in the updated *Guidelines* to assist population cancer registries to collect internationally consistent and comparable information on childhood cancer stage at diagnosis using available medical records.

General principles of the *Toronto Paediatric Cancer Stage Guidelines*[1]

1. *The Guidelines are intended for use by population registries only.*

   The staging systems recommended in the *Toronto Paediatric Cancer Stage Guidelines* are intended for use by population cancer registries. They are not intended to replace staging systems in clinical use nor to conflict with the stage used by clinicians in determining the treatment and prognosis of individual patients.

2. *Stage is a measure of extent of disease at diagnosis.*

   The staging systems described are intended to be a measure of the anatomic extent of disease at diagnosis. Stage is one of many prognostic indicators. Non-stage prognostic indicators that are important for patient management and risk assessment, such as tumour cytogenetics, may be collected by registries as resources permit,[2] however, for most of the disease groups outlined here, these items do not form part of the recommended staging systems.

3. *The goal is to derive the best estimate of stage.*

   The criteria provided herein are intended to enable registries to derive the best estimate of stage at diagnosis using available data sources. There are limitations inherent in collecting the data items required for staging from medical records and assumptions may be required. However, the criteria provided here will enable a reasonable and consistent measure of stage suitable for epidemiological analysis and stratified comparisons at a population level.

4. *Resource-specific tiered staging systems are endorsed.*

   The *Guidelines* endorse a two-tiered approach that provides less detailed criteria for registries with limited resources and data access (Tier 1) and more detailed criteria for well-resourced cancer registries (Tier 2). Tier 2 stage categories may be collapsed to Tier 1 categories to preserve comparability across registries.

Table 1: The Toronto Paediatric Cancer Stage Guidelines[1,2]

Diagnostic group/subgroup	**Tier 1 staging system** (for low resource settings)	**Tier 2 staging system** (for high resource settings)
Acute lymphoblastic leukaemia[5]	CNS negative	CNS1
	CNS positive	CNS2 CNS3
Hodgkin lymphoma[6]	Ann Arbor-stage IA/B Ann Arbor-stage IIA/B Ann Arbor-stage IIIA/B Ann Arbor-stage IVA/B	Ann Arbor-stage IA/B Ann Arbor-stage IIA/B Ann Arbor-stage IIIA/B Ann Arbor-stage IVA/B
Non-Hodgkin lymphoma[7]	Limited	St Jude/Murphy-stage I St Jude/Murphy-stage II St Jude/Murphy-stage III
	Advanced	St Jude/Murphy-stage IV
Neuroblastoma[8]	Localised Locoregional Metastatic INRGSS-MS disease	INRGSS-localised L1 INRGSS-locoregional L2 INRGSS-metastatic M INRGSS-MS disease
Renal tumours (except renal cell carcinomas)[9, 10]	Localised	Stage I/y-stage I Stage II/y-stage II Stage III/y-stage III
	Metastatic	Stage IV
Rhabdomyosarcoma[4]	Localised	TNM stage 1 TNM stage 2 TNM stage 3
	Metastatic	TNM stage 4
Non-rhabdomyosarcoma soft tissue sarcoma[4]	Localised	TNM stage 1 TNM stage 2 TNM stage 3
	Metastatic	TNM stage 4

Table 1 (cont.): The Toronto Paediatric Cancer Stage Guidelines[1,2]

Diagnostic group/subgroup	**Tier 1 staging system** (for low resource settings)	**Tier 2 staging system** (for high resource settings)
Malignant bone tumours[4]	Localised Metastatic	Localised Metastatic
	Localised	Localised
Retinoblastoma[11]	Localised	IRSS Stage 0 IRSS Stage I IRSS Stage II
	Regional	IRSS Stage III
	Metastatic	IRSS Stage IV
Hepatoblastoma[4]	Localised Metastatic	Localised Metastatic
Testicular cancer[4]	Localised Regional Metastatic	TNM stage I TNM stage II TNM stage III
Ovarian cancer[12]	Localised	FIGO stage I
	Regional	FIGO stage II FIGO stage III
	Metastatic	FIGO stage IV
Astrocytoma[4]	Localised Metastatic	Localised Metastatic
Medulloblastoma and other CNS embryonal tumours[13]	Localised	M0
	Metastatic	M1 M2 M3 M4
Ependymoma[13]	Localised	M0
	Metastatic	M1 M2 M3 M4

General rules of staging

1. Stage is defined as extent of disease at diagnosis and is based on evidence acquired before treatment (with the exception of renal tumours).

2. For all diagnostic groups including renal tumours, the presence of distant metastases is assessed clinically or pathologically before treatment.

3. If any of the information required for staging is missing from the medical record, stage is assessed as unknown.

4. If the relevant investigations were performed and there is no mention of a data item, then it should be assumed that the item is negative/absent; for example:
   - if there is no mention of metastases then assume '*no metastases';*
   - if there is no mention of nodal involvement, then assume '*no nodal involvement'*.

5. For those diagnostic groups where TNM is a component of staging, refer to 'The General Rules of the TNM System'.[4]

1. Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia
Tier 1 and Tier 2 are based on the extent of central nervous system (CNS) involvement. Tier 2 is the Children's Oncology Group (COG) staging system.[5]

Information required for staging	
TIER 1	**TIER 2**
- Clinical signs of CNS involvement (see definitions and notes) - Blasts in the cerebrospinal fluid (CSF) from cytospin	- Clinical signs of CNS involvement (see definitions and notes) - Blasts in the cerebrospinal fluid (CSF) from cytospin - White blood cell and red blood cell counts in the CSF from cytospin - White blood cell and red blood cell counts in the blood from blood tests

Definitions and notes
Blasts in the CSF - - Cytospin is required to determine the presence or absence of blasts in the CSF. - If blasts are referred to as "occasional" or "seen" or similar wording, assume blasts are present. - If there is no mention of blasts, assume blasts are absent. Clinical signs of CNS involvement include: - Cranial nerve palsy (e.g. facial weakness, ptosis), brain/eye involvement or hypothalamic syndrome. - Radiologic evidence of intracranial, intradural mass Extra-ocular orbital masses, severe headaches and eye swelling (in the absence of signs of cranial nerve involvement) are not sufficient to constitute CNS involvement.

<table>
<tr><th colspan="2">Staging criteria for acute lymphoblastic leukaemia</th></tr>
<tr><th>TIER 1</th><th>TIER 2</th></tr>
<tr><td>CNS-

• No clinical signs of CNS involvement
and no blasts in CSF</td><td>CNS1

• No clinical signs of CNS involvement
And no blasts in CSF</td></tr>
<tr><td rowspan="2">CNS+

• Clinical signs of CNS involvement

or

• blasts in CSF</td><td>CNS2

• No clinical signs of CNS involvement
and blasts in CSF
and either:

WBC < 5/µL CSF

or

WBC ≥5/µL CSF *and* RBC ≥ 10/µL CSF
and WBC/RBC in CSF ≤ 2x WBC/RBC in blood*</td></tr>
<tr><td>CNS3

• Clinical signs of CNS involvement

or

• Blasts in CSF
and WBC ≥ 5/µL CSF
and either:

RBC < 10/µL CSF

or

RBC ≥ 10/µL CSF
and WBC/RBC in CSF > 2x WBC/RBC in blood*</td></tr>
</table>

* Steinherz-Bleyer algorithm

Database entry codes for acute lymphoblastic leukaemia			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
CNS-	CNS-	**CNS1**	CNS1
CNS+	CNS+	**CNS2**	CNS2
		CNS3	CNS3
Unknown	X	**Unknown**	X

2. Hodgkin lymphoma

Hodgkin lymphoma
Tier 1 and Tier 2 are identical and follow the Ann Arbor staging system.[6, 14]

Information required for staging
Information required for Tier 1 and Tier 2 is the same: - Constitutional symptoms (see definitions and notes) - Diffuse or disseminated (multifocal) involvement of one or more extra-lymphatic organs - Distant disease: isolated (non-contiguous) extra-lymphatic organ involvement - Involvement of liver - Involvement of lungs - Bone marrow involvement, from bone marrow aspirate or biopsy - CSF involvement, from CSF examination - The number of lymph node regions involved, above and below the diaphragm, from imaging. Lymph node regions are listed in Figures 1a and 1b (see pages 16 and 17). - The number of extra-lymphatic organs or sites involved, above and below the diaphragm, from imaging

Definitions and notes
<u>Constitutional symptoms</u> The suffix A or B is added to the stage according to the absence or presence of defined constitutional symptoms, as follows: A = no constitutional symptoms are recorded, or the medical record states there are no constitutional symptoms B = medical record states there are constitutional symptoms Constitutional symptoms are: • *Fevers.* Unexplained fever with temperature above 38 degrees C (100.4 degrees F). • *Night sweats.* Drenching sweats (e.g. those that require change of bedclothes). • *Weight loss.* Unexplained weight loss of more than 10% of usual body weight in the 6 months prior to diagnosis.

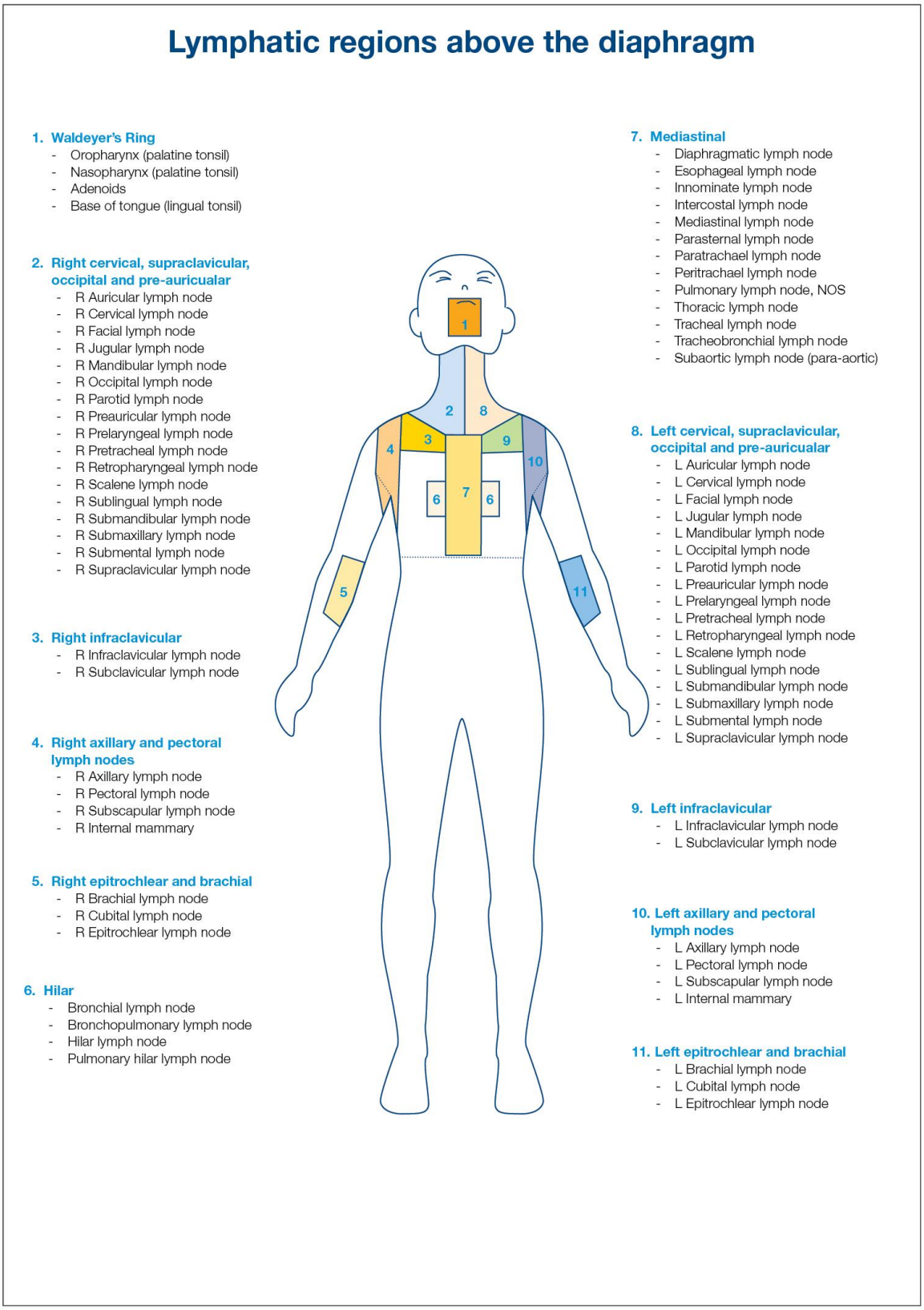


Figure 1a: Lymphatic regions above the diaphragm for the staging of Hodgkin's and Non-Hodgkin's Lymphoma

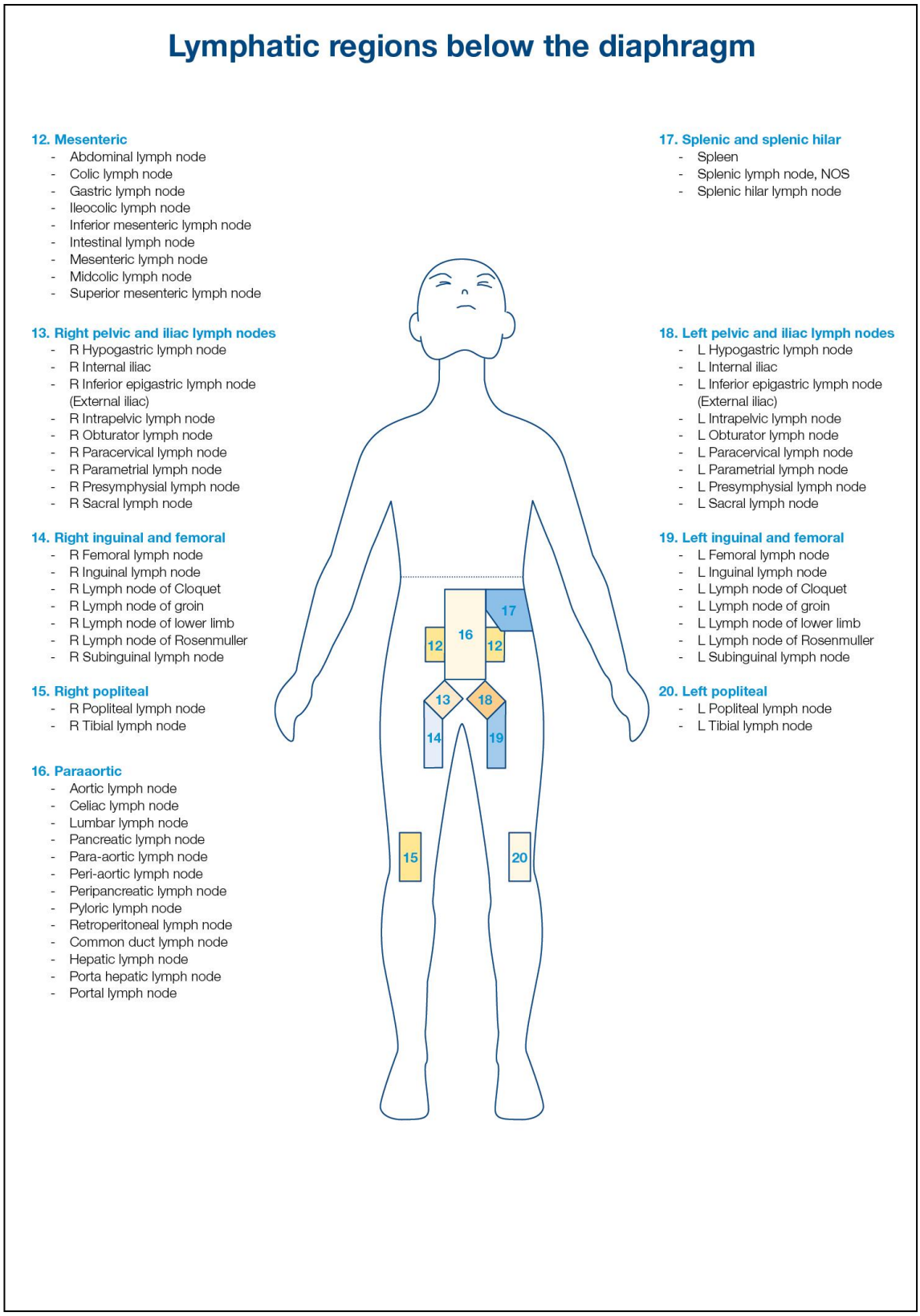


Figure 1b: Lymphatic regions below the diaphragm for the staging of Hodgkin's and Non-Hodgkin's Lymphoma

Staging criteria for Hodgkin lymphoma

The suffix **A** or **B** is added to the stage according to the absence or presence of defined constitutional symptoms, as follows:

A = no constitutional symptoms are recorded, or the medical record states there are no constitutional symptoms
B = medical record states there are constitutional symptoms

Constitutional symptoms are:

- *Fevers.* Unexplained fever with temperature above 38 degrees Celsius (100.4 degrees F).
- *Night sweats.* Drenching sweats (e.g. those that require change of bedclothes).
- *Weight loss.* Unexplained weight loss of more than 10% of usual body weight in the 6 months prior to diagnosis.

TIER 1	TIER 2
Stage I • Involvement of a single lymph node region or • Involvement of a single extra-lymphatic organ or site, without lymph node involvement.	**Stage I** • Involvement of a single lymph node region or • Involvement of a single extra-lymphatic organ or site, without lymph node involvement.
Stage II • Involvement of two or more lymph node regions on the SAME side (either above or below) of the diaphragm or • Localised involvement of a single extra-lymphatic organ or site in association with regional lymph node involvement (i.e. local extension from a lymph node area into a nearby organ), *with or without* involvement of other contiguous lymph node regions on the SAME side (either above or below) of the diaphragm.	**Stage II** • Involvement of two or more lymph node regions on the SAME side (either above or below) of the diaphragm or • Localised involvement of a single extra-lymphatic organ or site with associated regional lymph node involvement (i.e. local extension from a lymph node area into a nearby organ), *with or without* involvement of other contiguous lymph node regions on the SAME side (either above or below) of the diaphragm.
Stage III • Involvement of lymph node regions on BOTH sides (above and below) of the diaphragm. This may be accompanied by: - extra-lymphatic extension in association with adjacent lymph node involvement (i.e. local extension from a lymph node area into a nearby organ) and/or - involvement of spleen.	**Stage III** • Involvement of lymph node regions on BOTH sides (above and below) of the diaphragm. This may be accompanied by: - extra-lymphatic extension in association with adjacent lymph node involvement (i.e. local extension from a lymph node area into a nearby organ) and/or - involvement of spleen.

Stage IV • Diffuse or disseminated (multifocal) involvement of one or more extra-lymphatic organs with or without associated lymph node involvement or • Isolated (non-contiguous) extra-lymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). or • Any involvement of liver, bone marrow, lungs (except by direct extension from another site) or CSF.	**Stage IV** • Diffuse or disseminated (multifocal) involvement of one or more extra-lymphatic organs with or without associated lymph node involvement or • Isolated (non-contiguous) extra-lymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). or • Any involvement of liver, bone marrow, lungs (except by direct extension from another site) or CSF.

Database entry codes for Hodgkin lymphoma			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Stage IA	1A	**Stage IA**	1A
Stage IB	1B	**Stage IB**	1B
Stage IIA	2A	**Stage IIA**	2A
Stage IIB	2B	**Stage IIB**	2B
Stage IIIA	3A	**Stage IIIA**	3A
Stage IIIB	3B	**Stage IIIB**	3B
Stage IVA	4A	**Stage IVA**	4A
Stage IVB	4B	**Stage IVB**	4B
Unknown	X	**Unknown**	X

3. Non-Hodgkin lymphoma

Non-Hodgkin lymphoma
Tier 2 follows the St Jude/Murphy staging system.[7] Includes Burkitt lymphoma (diagnostic subgroup 2c).[15]

Information required for staging	
TIER 1	**TIER 2**
- Central nervous system (CNS) involvement (see definitions and notes). - Bone marrow involvement, from bone marrow aspiration or biopsy.	- Central nervous system (CNS) involvement (see definitions and notes). - Bone marrow involvement, from bone marrow aspiration or biopsy. - Involvement of tumour mass or nodal area in the abdomen and whether disease is extensive (unresectable). - Any primary intrathoracic tumours (mediastinal, hilar, pulmonary, pleural, or thymic). - Any paraspinal or epidural tumours. - Gastrointestinal tract tumour and whether it is completely resectable. - The number of lymph node regions involved, above and below the diaphragm, from imaging. Lymph node regions are listed in Figures 1a and 1b (see pages 16 and 17). - The number of extranodal organs or sites involved, above and below the diaphragm), from imaging.

Definitions and notes
CNS involvement: • Any CNS tumour mass (identified by imaging techniques [ie, CT, MRI]); or • Cranial nerve palsy that cannot be explained by extradural lesions; or • Blasts morphologically identified in CSF. (In the absence of a CNS tumour mass and cranial nerve palsy, a CSF report is required to confirm or exclude CNS involvement.) BM involvement: • Morphologic evidence of ≥ 5% blasts or lymphoma cells by BM aspiration or biopsy.

Staging criteria for non-Hodgkin lymphoma	
TIER 1	**TIER 2**
Limited • No involvement of CNS *and* no involvement of bone marrow.	**Stage I** • Involvement of a single tumour mass or nodal area, excluding the abdomen and mediastinum.
	Stage II • A single tumour (extranodal) with regional node involvement or • Two or more nodal areas on the SAME side (either above or below) of the diaphragm or • Two or more single (extranodal) tumours, with or without regional node involvement, on the SAME side (either above or below) of the diaphragm or • A completely resected primary gastrointestinal tract tumour with or without involvement of associated mesenteric nodes only.
	Stage III • Tumours (extranodal) or nodal areas on BOTH sides (above and below) of the diaphragm or • Any primary intrathoracic tumours (mediastinal, hilar, pulmonary, pleural, or thymic). or • Extensive* (unresectable) primary intra-abdominal disease or • Any paraspinal or epidural tumours regardless of other tumour sites.
Advanced • Involvement of CNS and/or bone marrow	**Stage IV** • Initial CNS and/or bone marrow involvement.

* Extensive disease typically exhibits spread to para-aortic and retro-peritoneal areas by implants and plaques in mesentery or peritoneum, or by direct infiltration of structures adjacent to the primary tumour. Ascites may be present, and complete resection of all gross tumour is not possible.

Database entry codes for non-Hodgkin lymphoma			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Limited	L	**Stage I**	1
		Stage II	2
		Stage III	3
Advanced	A	**Stage IV**	4
Unknown	X	**Unknown**	X

4. Neuroblastoma

Neuroblastoma
Tier 2 follows the International Neuroblastoma Risk Group Staging System (INRGSS).[8] Tier 1 criteria are simplified proxies of Tier 2 that do not require assessment of image-defined risk factors for use in settings where cross-sectional imaging is not available.

Information required for staging	
TIER 1	**TIER 2**
- Age of the case in months/days - Distant metastatic disease - Site of metastases (skin, liver or bone marrow) - Locoregional spread	- Age of the case in months/days - Distant metastatic disease - Site of metastases (skin, liver or bone marrow) - Number of image-defined risk factors (see definitions and notes below) - MIBG scintigraphy for bone/bone marrow

Definitions and notes
Patients with multifocal primary tumours should be staged according to the greatest extent of disease as defined in the IDRF table. <u>Image-defined risk factors</u> Staging requires assessment of whether or not patients have none (Stage L1) or one or more (Stage L2) of the image-defined risk factors (IDRF) listed below. These are identified in reports of imaging at diagnosis, prior to any surgical resection. - *Ipsilateral tumour extension within two body compartments* Neck-chest, chest-abdomen, abdomen-pelvis - *Neck* Tumour encasing carotid and/or vertebral artery and/or internal jugular vein Tumour extending to base of skull Tumour compressing the trachea - *Cervico-thoracic junction* Tumour encasing brachial plexus roots Tumour encasing subclavian vessels and/or vertebral and/or carotid artery Tumour compressing the trachea - *Thorax* Tumour encasing the aorta and/or major branches Tumour compressing the trachea and/or principal bronchi Lower mediastinal tumour, infiltrating the costo-vertebral junction between T9 and T12 - *Thoraco-abdominal* Tumour encasing the aorta and/or vena cava - *Abdomen/pelvis* Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament Tumour encasing branches of the superior mesenteric artery at the mesenteric root Tumour encasing the origin of the coeliac axis, and/or of the superior mesenteric artery Tumour invading one or both renal pedicles Tumour encasing the aorta and/or vena cava Tumour encasing the iliac vessels Pelvic tumour crossing the sciatic notch - *Intraspinal tumour extension whatever the location provided that:* More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary eptomeningeal spaces are not visible and/or the spinal cord signal is abnormal - *Infiltration of adjacent organs/structures* Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery

Staging criteria for neuroblastoma			
TIER 1		**TIER 2**	
Localised	Localised tumour not involving vital structures and confined to one body compartment	**Stage L1**	Localised tumour that does not involve any vital structures as defined by the list of IDRFs (i.e. there are no IDRFs) and the tumour must be confined within one body compartment, neck, chest, abdomen, or pelvis. An intraspinal tumour extension that does not fulfil the criteria for an IDRF is consistent with stage L1.
Locoregional	Locoregional tumour with spread	**Stage L2**	Locoregional tumour with one or more IDRFs. The tumour may be ipsilaterally contiguous within body compartments (ie, a left sided abdominal tumour with left-sided lung, bone or pleura involvement should be considered stage L2). However, a clearly left sided abdominal tumour with right-sided lung, bone or pleura (or vice versa) involvement is defined as metastatic disease.
Metastatic	Distant metastatic disease (except stage MS)	**Stage M**	Distant metastatic disease (ie, not contiguous with the primary tumour) except as defined for stage MS. Nonregional (distant) lymph node involvement is metastatic disease. However, an upper abdominal tumour with enlarged lower mediastinal nodes or a pelvic tumour with inguinal lymph node involvement is considered locoregional disease. Ascites and/or a pleural effusion, even with malignant cells, do not constitute metastatic disease unless they are remote from the body compartment of the primary tumour.
MS	Metastatic disease confined to skin, liver, and/or bone marrow in a patient less than 18 months (547 days)	**Stage MS**	Metastatic disease confined to skin, liver, and/or bone marrow, in a patient less than 18 months (547 days). MIBG scintigraphy must be negative in bone and bone marrow.

Database entry codes for neuroblastoma			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Stage L1**	L1
Locoregional	LR	**Stage L2**	L2
Metastatic	M	**Stage M**	M
MS	MS	**Stage MS**	MS
Unknown	X	**Unknown**	X

5. Renal tumours (excluding renal cell carcinomas)

Renal tumours (excluding renal cell carcinomas)
Two principal staging systems exist for renal tumours.[9, 10] Both systems are based on findings at surgery (except for stage IV which is based on presence of distant metastases at diagnosis). The COG/National Wilms Tumour Study Group (NWTSG) staging system is based on findings at surgery for patients who have not received chemotherapy prior to surgery. The SIOP staging system is based on findings at surgery for patients who have received chemotherapy prior to surgery. The recommended staging system incorporates both systems; "y" designates SIOP stage (for patients who have received neo-adjuvant chemotherapy). It is noted that giving chemotherapy before surgery will shrink the tumour and will likely "downstage" the patient.

Information required for staging	
TIER 1	**TIER 2**
- Distant metastases	- Treatment protocol – COG or SIOP - Distant metastases - Involvement of abdominal lymph nodes - Biopsy (including fine needle aspiration) prior to resection (COG protocol) - Biopsy (excluding fine needle aspiration) prior to resection (SIOP protocol) - Complete excision of tumour - Tumour confined to kidney

Definitions and notes
In cases of bilateral disease - the presence of synchronous disease should be noted - for purpose of staging, only the most advanced kidney should be recorded. At diagnosis, if diagnostic imaging reports on the status of the liver, lung, bone, brain and other sites and mentions the words "suspicious", "highly suspicious", "possible" or "highly suspected", record as metastatic disease (stage IV) regardless of upfront surgery or chemotherapy. Note that the majority of renal tumours in childhood are Wilms tumours.

Staging criteria for renal tumours (excluding renal cell carcinoma) based on findings at surgery for patients who <u>have not</u> received chemotherapy prior to surgery (Children's Oncology Group (COG) protocol)	
TIER 1	**TIER 2**
Localised Tumour confined to area of origin including abdominal lymph nodes	**Stage I** Tumour is limited to the kidney and completely excised: • Renal capsule intact, not penetrated by tumour • No tumour invasion of veins or lymphatics of renal sinus • No nodal or haematogenous metastases • No prior biopsy • Negative margins
	Stage II Tumour extends beyond kidney but completely resected: • Tumour penetrates renal capsule • Tumour in lymphatics or veins of renal sinus • Tumour in renal vein with margin not involved • No nodal or haematogenous metastases • Negative margins
	Stage III Residual tumour or nonhaematogenous metastases confined to abdomen: • Involved abdominal nodes • Peritoneal contamination or tumour implant • Tumour spillage of any degree occurring before or during surgery • Gross residual tumour in abdomen • Biopsy of tumour (including fine-needle aspiration) prior to removal of kidney • Resection margins involved by tumour
Metastatic Distant metastases present at diagnosis	**Stage IV** Haematogenous metastases or spread beyond abdomen <u>at diagnosis</u>

<table>
<tr><th colspan="2">Staging criteria for renal tumours (excluding renal cell carcinoma)
based on findings at surgery for patients who <u>have</u> received chemotherapy prior to surgery
(International Society of Paediatric Oncology (SIOP) protocol)</th></tr>
<tr><th>TIER 1</th><th>TIER 2</th></tr>
<tr><td rowspan="3">Localised

Tumour confined to area of origin including abdominal lymph nodes</td><td>Stage y-I

Tumour limited to kidney and completely resected:
Renal capsule may be infiltrated by tumour, but tumour does not reach the outer surface
Tumour may protrude or bulge into the pelvic system or ureter, but does not infiltrate
Vessels of renal sinus not involved</td></tr>
<tr><td>Stage y-II

Tumour extends beyond kidney but completely resected:
Tumour penetrates renal capsule into perirenal fat
Tumour infiltrates the renal sinus and/or invades blood and lymphatic vessels outside renal parenchyma but is completely resected
Tumour infiltrates adjacent organs or vena cava but is completely resected</td></tr>
<tr><td>Stage y-III

Incomplete excision of the tumour (gross or microscopic extension beyond the resection margins):
Involved abdominal lymph nodes, including necrotic tumour or chemotherapy-induced changes
Tumour rupture before or intraoperatively
Tumour has penetrated the peritoneal surface
Tumour thrombi present at resection margins
Surgical biopsy prior to resection (does not include needle biopsy)</td></tr>
<tr><td>Metastatic

Distant metastases present at diagnosis</td><td>Stage IV

Haematogenous metastases or spread beyond abdomen <u>at diagnosis</u>.</td></tr>
</table>

Database entry codes for renal tumours (excluding renal cell carcinoma)			
Children's Oncology Group (COG) protocol (prechemotherapy)			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Stage I**	1
		Stage II	2
		Stage III	3
Metastatic	M	**Stage IV**	4
Unknown	X	**Unknown**	X

Database entry codes for renal tumours (excluding renal cell carcinoma)			
International Society of Paediatric Oncology (SIOP) protocol (postchemotherapy)			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Stage y-I**	y1
		Stage y-II	y2
		Stage y-III	y3
Metastatic	M	**Stage IV**	4
Unknown	X	**Unknown**	X

6. Rhabdomyosarcoma

Rhabdomyosarcoma
Tier 2 follows a modified TNM classification incorporating anatomic site of disease. [4]

Information required for staging	
TIER 1	**TIER 2**
- Distant metastases	- Distant metastases - Regional lymph node involvement - Tumour size - Tumour site (favourable or unfavourable)

Definitions and notes

Favourable and unfavourable anatomic sites of disease

Favourable anatomic sites:
- orbit
- head and neck (excluding parameningeal)
  - scalp
  - parotid
  - oral cavity
  - larynx
  - oropharynx
  - cheek
  - hypopharynx
  - thyroid and parathyroid
  - neck
- genitourinary sites (excluding bladder and prostate tumours)
- gallbladder and bile ducts

Unfavourable anatomic sites:
- bladder
- prostate
- extremity
- parameningeal
  - middle ear
  - nasal cavity
  - paranasal sinuses (including tumours that extend into the paranasal sinus)
  - nasopharynx
  - infratemporal fossa/pterygopalatine
  - parapharyngeal area
- trunk
- retroperitoneum
- all other sites not noted as favourable

T – Tumour size

T0 = no evidence of primary tumour
T1 = tumour confined to a single anatomic site
T1a = tumour ≤ 5cm in greatest dimension
T1b = tumour > 5cm in greatest dimension
T2 = extension beyond anatomic site
T2a = tumour ≤ 5cm in greatest dimension
T2b = tumour > 5cm in greatest dimension
Tx = primary tumour cannot be assessed

N - Regional nodes

N0 = regional lymph nodes not involved
N1 = regional lymph nodes involved
Nx = regional lymph nodes cannot be assessed (especially sites that preclude lymph node evaluation)

M - Metastases

M0 = no distant metastasis
M1 = distant metastasis

Staging criteria for rhabdomyosarcoma			
TIER 1		**TIER 2**	
Localised	Tumour confined to the area of origin including the regional lymph nodes.	**Stage I**	Favourable site and Any T Any N M0
		Stage II	Unfavourable site and T1a, T2a N0 M0
		Stage III	Unfavourable site and T1a, T2a N1 M0 T1b, T2b Any N M0
Metastatic	Distant metastases present	**Stage IV**	Any site Any T Any N M1

Database entry codes for rhabdomyosarcoma			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Stage I**	1
		Stage II	2
		Stage III	3
Metastatic	M	**Stage IV**	4
Unknown	X	**Unknown**	X

7. Non-rhabdomyosarcoma soft tissue sarcoma

Non-rhabdomyosarcoma soft tissue sarcoma
Tier 2 follows a modified TNM classification incorporating tumour grade.[4]

Information required for staging	
TIER 1	**TIER 2**
- Distant metastases	- Distant metastases - Regional lymph node involvement - Tumour size - Tumour grade

Definitions and notes
<u>T - Tumour</u> T0 No evidence of primary tumour T1 Tumour ≤ 5cm in greatest dimension T2 Tumour > 5cm and ≤ 10cm in greatest dimension T3 Tumour >10cm and ≤ 15cm in greatest dimension T4 Tumour >15cm in greatest dimension Tx Primary tumour cannot be assessed <u>N - Regional lymph nodes</u> N0 = regional lymph nodes not involved N1 = regional lymph nodes involved Nx = regional lymph nodes cannot be assessed (especially sites that preclude lymph node evaluation) <u>M - Metastases</u> M0 = no distant metastasis M1 = metastasis present <u>G – Grade</u> G1 = grade 1 (low/well differentiated) G2 = grade 2 (intermediate/moderately differentiated) G3 = grade 3 (high/poorly/undifferentiated) Gx = grade cannot be assessed

Staging criteria for non-rhabdomyosarcoma soft tissue sarcoma			
TIER 1		**TIER 2**	
Localised	Tumour confined to the area of origin including regional lymph nodes.	**Stage I**	Any T N0 M0 G1 or Gx
		Stage II	T1 N0 M0 G2 or G3
		Stage III	T2 or T3 or T4 N0 M0 G2 or G3 *or* Any T N1 M0 Any G (G1, G2, G3 or Gx)
Metastatic	Distant metastases present	**Stage IV**	Any T Any N M1 Any G (G1, G2, G3, Gx)

Database entry codes for non-rhabdomyosarcoma soft tissue sarcoma			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Stage I**	1
		Stage II	2
		Stage III	3
Metastatic	M	**Stage IV**	4
Unknown	X	**Unknown**	X

8. Malignant bone tumours

Malignant bone tumours
Only two stages are recommended (localised or metastatic) for both Tier 1 and Tier 2.[4]

Information required for staging
Information required for Tier 1 and Tier 2 is the same: - distant metastases

Definitions and notes
"Skip lesions", "skip metastases" or "seeding" in the same bone as the primary tumour are considered localised and not metastatic; if in a different bone to the primary tumour these are considered metastatic.

Staging criteria for malignant bone tumours			
TIER 1		**TIER 2**	
Localised	Tumour confined to the area of origin including regional lymph nodes	**Localised**	Tumour confined to the area of origin including regional lymph nodes
Metastatic	Distant metastases present	**Metastatic**	Distant metastases present

Database entry codes for malignant bone tumours			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Localised**	L
Metastatic	M	**Metastatic**	M
Unknown	X	**Unknown**	X

9. Retinoblastoma

Retinoblastoma
Tier 2 follows the International Retinoblastoma Staging System (IRSS).[11] Tier 2 stage is determined after enucleation and is therefore a pathological classification.

Information required for staging	
TIER 1	**TIER 2**
- Distant metastases - Involvement of the orbit - Involvement of regional lymph nodes	- Distant metastases - Involvement of the orbit - Involvement of regional lymph nodes - Enucleation - Residual disease in surgical margins

Definitions and notes
In cases of bilateral disease: - the presence of synchronous disease should be noted - for purpose of stage, only the most advanced eye should be recorded.

Staging criteria for retinoblastoma			
TIER 1		**TIER 2**	
Localised	Intraocular	**Stage 0**	The tumour is confined to the globe. Enucleation has not been performed. (The patient is treated "conservatively" with either focal therapies or chemotherapy.)
		Stage I	Enucleation with negative margins
		Stage II	Enucleation with microscopic residual disease
Regional	Orbital extension or regional lymph nodes	**Stage III**	Regional extension: involvement of the orbit and/or preauricular or cervical lymph node extension
Metastatic	Distant metastases present	**Stage IV**	Distant metastatic disease

Database entry codes for retinoblastoma			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Stage 0**	0
		Stage I	1
		Stage II	2
Regional	R	**Stage III**	3
Metastatic	M	**Stage IV**	4
Unknown	X	**Unknown**	X

10. Hepatoblastoma

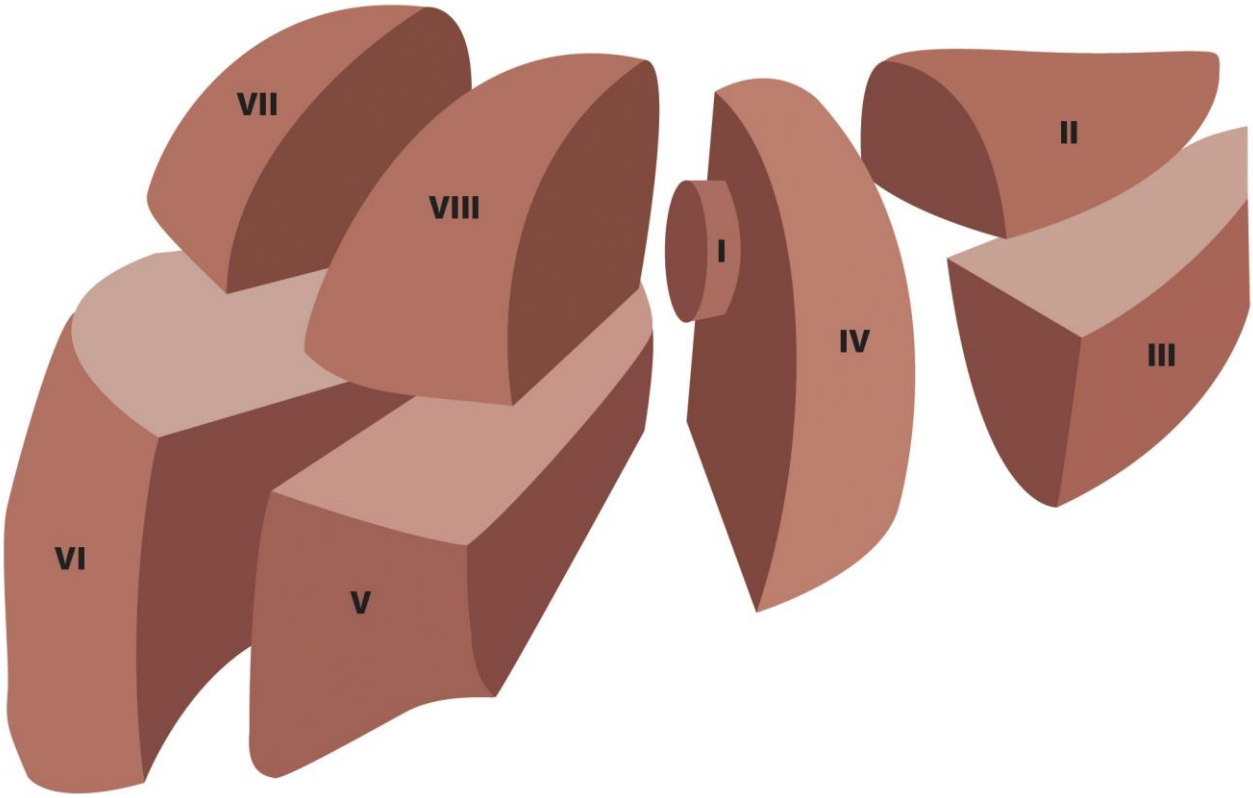
Hepatoblastoma
Only two stages are recommended for Tier 1 - localised or metastatic.[4] In addition to localised and metastatic, Tier 2 also incorporates the PRETEXT number.[16, 17]

Information required for staging	
TIER 1	**TIER 2**
- Distant metastases	- Distant metastases - Segments of the liver that are involved, determined by imaging.

Definitions and notes
The PRETEXT number describes the intrahepatic extent of the primary tumour before any therapy. Further details of how to assign the PRETEXT number are shown on the following pages.

Segmentation of the liver
(exploded front view)

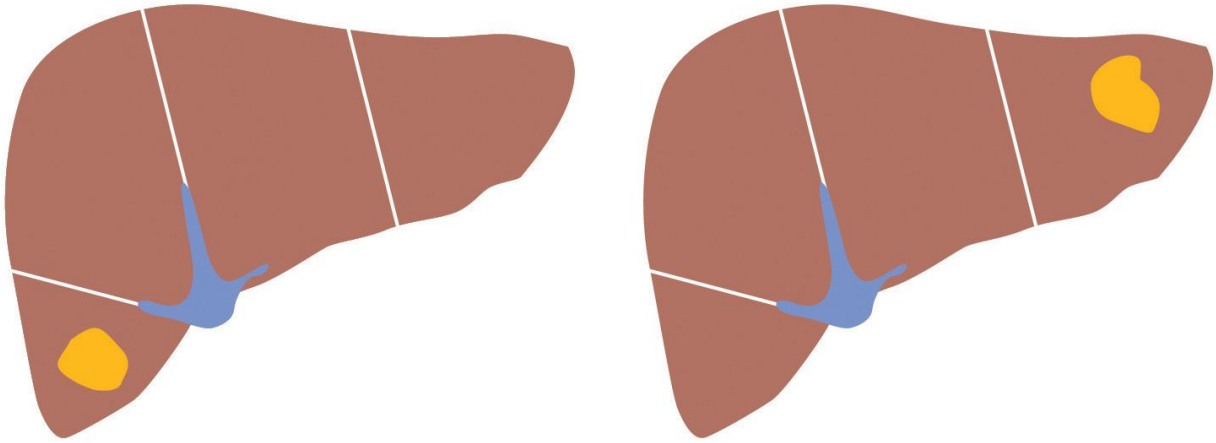
Caudate lobe
I Caudate lobe
Left lateral section
II Left lateral superior segment
III Left lateral inferior segment
Left medial section
IV Left medial segment
Right anterior section
V Right anterior inferior segment
VIII Right anterior superior segment
Right posterior section
VI Right posterior inferior segment
VII Right posterior superior segment



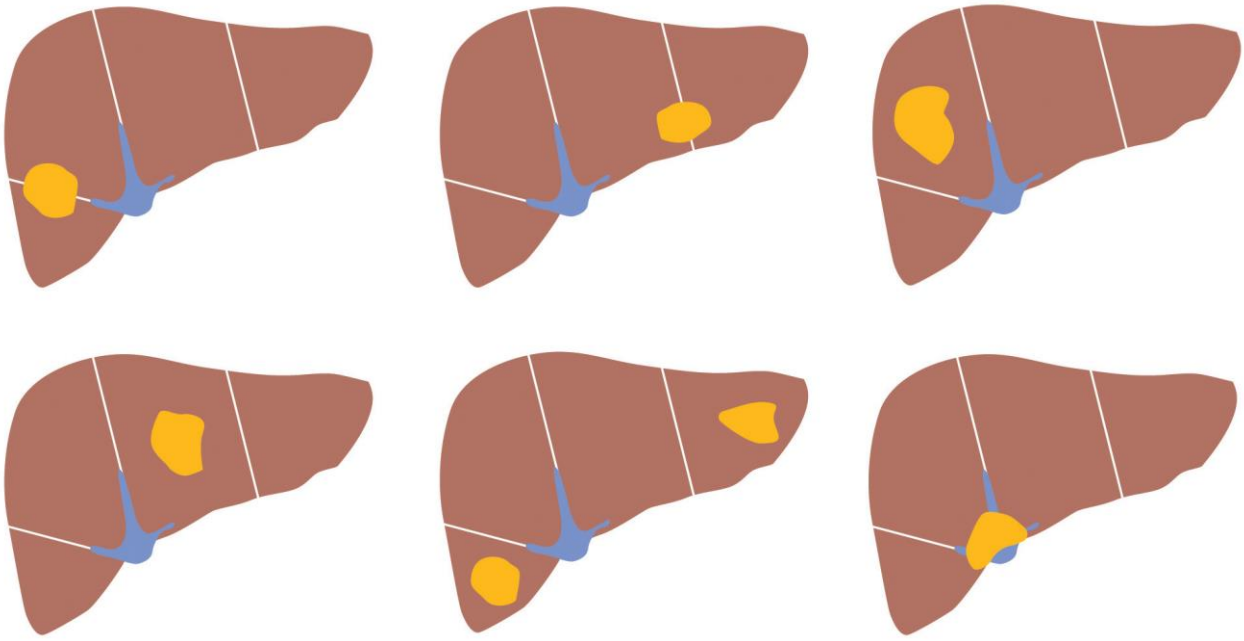
Definitions of PRETEXT number

(diagrams represent transverse section of the liver)

Pretext I: One section is involved by tumour and <u>three adjoining sections are free</u>.

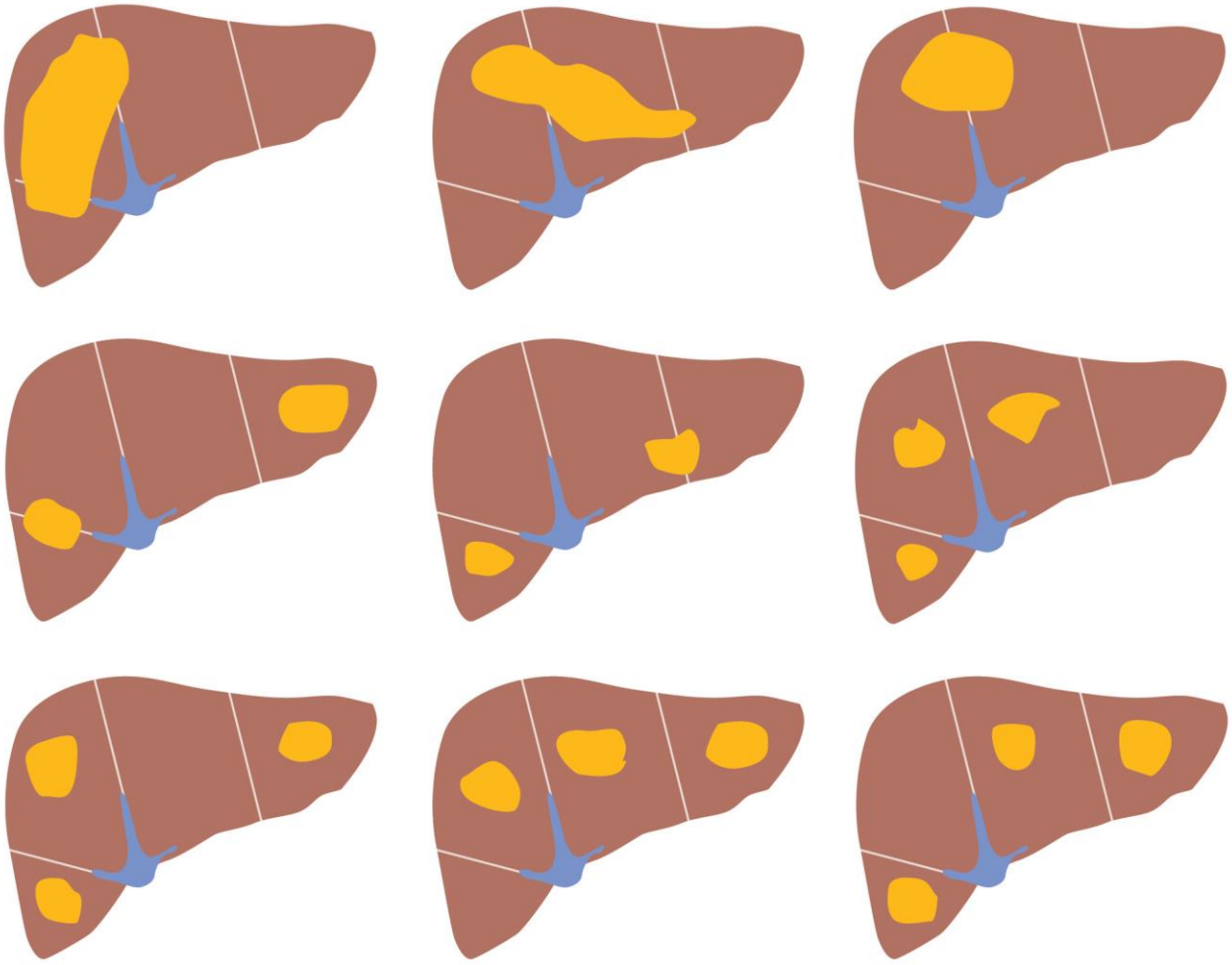


Pretext II: One or two sections are involved by tumour, but <u>two adjoining sections are free</u>. Tumours limited to the caudate lobe only are also classified as PRETEXT II.

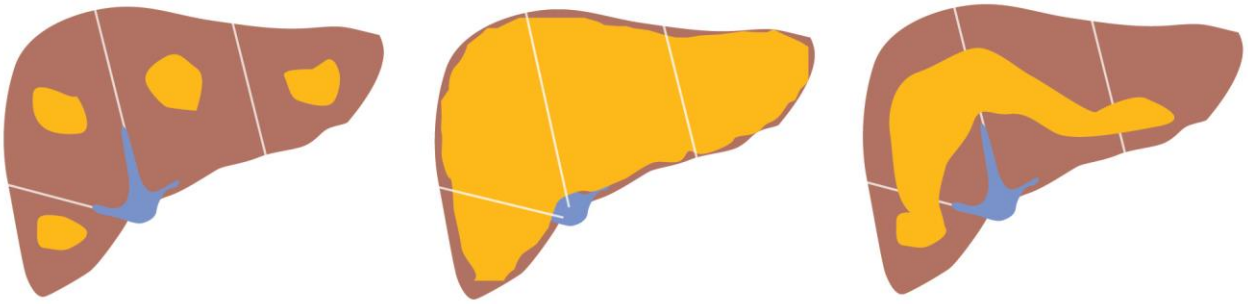


Figures adapted from Towbin et. al.[17]

Pretext III: Two or three sections are involved by tumour, and no two adjoining sections are free.



Pretext IV: All four sections are involved by tumour.



Figures adapted from Towbin et. al.[17]

Staging criteria for hepatoblastoma			
TIER 1		**TIER 2**	
Localised	Tumour confined to the liver including regional lymph nodes	**Localised**	Tumour confined to the liver including regional lymph nodes
		PRETEXT	
		I	One section of the liver is involved and three adjoining sections are free
		II	One or two sections of the liver are involved, but two adjoining sections are free OR Caudate lobe only is involved
		III	Two or three sections of the liver are involved, and no two adjoining sections are free
		IV	All four sections of the liver are involved
Metastatic	Distant metastases present	**Metastatic**	Distant metastases present
		PRETEXT	
		I	One section of the liver is involved and three adjoining sections are free
		II	One or two sections of the liver are involved, but two adjoining sections are free OR Caudate lobe only is involved
		III	Two or three sections of the liver are involved, and no two adjoining sections are free
		IV	All four sections of the liver are involved

Database entry codes for hepatoblastoma			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Localised, PRETEXT I**	L1
		Localised, PRETEXT II	L2
		Localised, PRETEXT II	L3
		Localised, PRETEXT IV	L4
		Localised, PRETEXT unknown	LX
Metastatic	M	**Metastatic, PRETEXT I**	M1
		Metastatic, PRETEXT II	M2
		Metastatic, PRETEXT III	M3
		Metastatic, PRETEXT IV	M4
		Metastatic, PRETEXT unknown	MX
Unknown	X	**Unknown, PRETEXT I**	X and PRETEXT 1
		Unknown, PRETEXT II	X and PRETEXT 2
		Unknown, PRETEXT III	X and PRETEXT 3
		Unknown, PRETEXT IV	X and PRETEXT 4
		Unknown, PRETEXT unknown	X and PRETEXT X

11. Testicular germ cell tumours

Testicular germ cell tumours
Tier 2 follows the TNM classification.[4]

Information required for staging	
TIER 1	**TIER 2**
- Distant metastases - Involvement of regional lymph nodes	- Distant metastases - Involvement of regional lymph nodes - Size of regional lymph node mass - Extent of primary tumour - Serum tumour levels from pathology reports for: LDH (lactate dehydrogenase) hCG (human chorionic gonadotropin) AFP (alpha-fetoprotein)

Definitions and notes
T - Tumour The extent of primary tumour is usually classified after radical orchiectomy, and for this reason, a pathologic stage is assigned.
pTx Primary tumour cannot be assessed
pT0 No evidence of primary tumour (e.g. histologic scar in testis)
pT1 Tumour limited to the testis and epididymis without vascular/lymphatic invasion; tumour may invade into the tunica albuginea but not the tunica vaginalis
pT2 Tumour limited to the testis and epididymis with vascular/lymphatic invasion, or tumour extending through the tunica albuginea with involvement of the tunica vaginalis
pT3 Tumour invades the spermatic cord with or without vascular/lymphatic invasion
pT4 Tumour invades the scrotum with or without vascular/lymphatic invasion
* Note: Except for pT4, extent of primary tumour is classified by radical orchiectomy. Tx is used if radical orchiectomy has not been performed.
N - Regional nodes
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis with a lymph node mass 2cm or less in greatest dimension; or multiple lymph nodes, none more than 2cm in greatest dimension.
N2 Metastasis with a lymph node mass more than 2cm but not more than 5cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2cm but not more than 5cm in greatest dimension.
N3 Metastasis with a lymph node mass more than 5cm in greatest dimension
pN - Pathologic regional nodes
pNx Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis with a lymph node mass 2cm or less in greatest dimension and five or fewer positive nodes, none more than 2cm in greatest dimension
pN2 Metastasis with a lymph node mass more than 2cm but not more than 5cm in greatest dimension; or more than five nodes positive, none more than 5cm; or evidence of extranodal extension of tumour
pN3 Metastasis with a lymph node mass more than 5cm in greatest dimension
M – Distant metastasis
M0 No distant metastasis
M1 Distant metastasis
S – Serum tumour markers
SX Serum marker studies not available or not performed
S0 Serum marker study levels within normal limits[18] i.e. LDH between 1.5-3.2 ukat/l AND hCG <5 mIU/ml AND AFP <40 ng/ml
S1 LDH <1.5 x normal OR hCG 5-5000 mIU/ml OR AFP 40-1000 ng/ml
S2 LDH 1.5-10 x normal OR hCG 5000-50000 mIU/ml OR AFP 1000-10000 ng/ml
S3 LDH >10 x normal OR hCG >50000 mIU/ml OR AFP >10000 ng/ml

Staging criteria for testicular germ cell tumours			
TIER 1		**TIER 2**	
Localised	Tumour confined to the testes	**Stage I**	pT1-4, N0, M0, SX
		Stage IA	pT1, N0, M0, S0
		Stage IB	pT2-4, N0, M0, S0
Regional	Tumour extension to regional lymph nodes: - Interaortocaval - Para-aortic (periaortic) - Paracaval - Preaortic - Precaval - Retroaortic - Retrocaval - Along spermatic cord	**Stage IS**	Any pT, N0, M0, S1-3
		Stage II	Any pT, N1-3, M0, SX
		Stage IIA	Any pT, N1, M0, S0,S1
		Stage IIB	Any pT, N2, M0, S0,S1
		Stage IIC	Any pT, N3, M0, S0,S1
Metastatic	Distant metastases present	**Stage III**	Any pT, Any N, M1, SX
		Stage IIIA	Any pT, Any N, M1, S0,S1
		Stage IIIB	Any pT, N1-N3, M0, S2 OR Any pT, Any N, M1, S2
		Stage IIIC	Any pT, N1-N3, M0, S3 OR Any pT, Any N, M1, S3

Database entry codes for testicular germ cell tumours			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Stage I**	1
		Stage IA	1A
		Stage IB	1B
Regional	R	**Stage IS**	1S
		Stage II	2
		Stage IIA	2A
		Stage IIB	2B
		Stage IIC	2C
Metastatic	M	**Stage III**	3
		Stage IIIA	3A
		Stage IIIB	3B
		Stage IIIC	3C
Unknown	X	**Unknown**	X

12. Ovarian germ cell tumours

Ovarian germ cell tumours
Tier 2 follows the FIGO staging system.[12]

Information required for staging	
TIER 1	**TIER 2**
- Distant metastases - Involvement of retroperitoneal lymph nodes - Extent of tumour	- Distant metastases - Involvement of retroperitoneal lymph nodes - Extent of tumour (cytologically or histologically confirmed)

Staging criteria for ovarian germ cell tumours			
TIER 1		**TIER 2**	
Localised	Tumour confined to ovaries	**Stage I**	Tumour confined to ovaries (one or both)
Regional	Tumour involves one or both ovaries with pelvic extension and/or spread to the peritoneum outside the pelvis and/or retroperitoneal lymph nodes	**Stage II**	Tumour involves one or both ovaries with pelvic extension (below the pelvic brim)
		Stage III	Tumour involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
Metastatic	Distant metastatic disease excluding peritoneal metastases	**Stage IV**	Distant metastasis (excludes peritoneal metastases)

Database entry codes for ovarian germ cell tumours			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Stage I**	1
Regional	R	**Stage II**	2
		Stage III	3
Metastatic	M	**Stage IV**	4
Unknown	X	**Unknown**	X

13. Astrocytomas

Astrocytomas
Only two stages are recommended (localised or metastatic) for both Tier 1 and Tier 2.[4] Tumours with non-malignant behaviour are included.

Information required for staging
Information required for Tier 1 and Tier 2 is the same: **-** distant metastases

Staging criteria for astrocytomas			
TIER 1		**TIER 2**	
Localised	Localised disease	**Localised**	Localised disease
Metastatic	Distant metastases present	**Metastatic**	Distant metastases present

Database entry codes for astrocytomas			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**Localised**	L
Metastatic	M	**Metastatic**	M
Unknown	X	**Unknown**	X

14. Medulloblastoma and other CNS embryonal tumours

Medulloblastoma	
Tier 2 follows the M staging system.[13] Tumours with non-malignant behaviour are included.	
Information required for staging	
TIER 1	**TIER 2**
- Distant metastases - Tumour cells in the cerebrospinal fluid	- Distant metastases - Metastatic site from imaging - Tumour cells in the cerebrospinal fluid

Staging criteria for medulloblastoma			
TIER 1		**TIER 2**	
Localised	Localised disease	**M0**	No visible disease on imaging (MRI brain and spine) beyond primary site of disease and no tumour cells in the cerebrospinal fluid (CSF)
Metastatic	Disease beyond local site (e.g., other lesions in brain or spine OR tumour cells in CSF OR distant metastases).	**M1**	Tumour cells in the CSF
		M2	Visible metastasis in brain
		M3	Visible metastasis in spine or Visible metastasis in cervicomedullary (junction)
		M4	Metastasis outside of the central nervous system

Database entry codes for medulloblastoma			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**M0**	M0
Metastatic	M	**M1**	M1
		M2	M2
		M3	M3
		M4	M4
Unknown	X	**Unknown**	X

15. Ependymoma

Ependymoma	
Tier 2 follows the M staging system.[13] Tumours with non-malignant behaviour are included.	
Information required for staging	
TIER 1	**TIER 2**
- Distant metastases - Tumour cells in the cerebrospinal fluid	- Distant metastases - Metastatic site from imaging - Tumour cells in the cerebrospinal fluid

Staging criteria for ependymoma			
TIER 1		**TIER 2**	
Localised	Localised disease	**M0**	No visible disease on imaging (MRI brain and spine) beyond primary site of disease and no tumour cells in the cerebrospinal fluid (CSF)
Metastatic	Disease beyond local site (e.g., other lesions in brain or spine OR tumour cells in CSF OR distant metastases).	**M1**	Tumour cells in the CSF
		M2	Visible metastasis in brain
		M3	Visible metastasis in spine or Visible metastasis in cervicomedullary (junction)
		M4	Metastasis outside of the central nervous system

Database entry codes for ependymoma			
TIER 1		**TIER 2**	
Stage	**Code**	**Stage**	**Code**
Localised	L	**M0**	M0
Metastatic	M	**M1**	M1
		M2	M2
		M3	M3
		M4	M4
Unknown	X	**Unknown**	X

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