Paediatric cancer stage in population-based cancer registries: the Toronto consensus principles and guidelines

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Population-based cancer registries generate estimates of incidence and survival that are essential for cancer surveillance, research, and control strategies. Although data on cancer stage allow meaningful assessments of changes in cancer incidence and outcomes, stage is not recorded by most population-based cancer registries. The main method of staging adult cancers is the TNM classification. The criteria for staging paediatric cancers, however, vary by diagnosis, have evolved over time, and sometimes vary by cooperative trial group. Consistency in the collection of staging data has therefore been challenging for population-based cancer registries. We assembled key experts and stakeholders (oncologists, cancer registrars, epidemiologists) and used a modified Delphi approach to establish principles for paediatric cancer stage collection. In this Review, we make recommendations on which staging systems should be adopted by population-based cancer registries for the major childhood cancers, including adaptations for low-income countries. Wide adoption of these guidelines in registries will ease international comparative incidence and outcome studies.

Introduction

Population-based cancer registries are a unique resource for both cancer researchers and policy makers.[1] Registry data have been used for disease surveillance and to derive population-based estimates of incidence, prevalence, and outcome in both adults and children.[2–5] The results of these investigations have been used to plan and evaluate national cancer control strategies.[1,3,6,7] Cancer stage is a core concept in oncology, providing a "common nomenclature on which to base cancer management, research and information exchange".[8,9] Accurate stage data are crucial when comparing cancer outcomes between groups or over time. Despite this, many population-based cancer registries either do not record stage data at all or, in paediatric patients, record stage according to the adult TNM staging classification. The TNM classification was developed by the Union for International Cancer Control, and is used to classify and code stage in many adult malignant diseases, but is not applicable to most paediatric cancers.[8]

Because of their heterogeneity and rarity, childhood cancers already represent a particular data management challenge for registries.[10] Most childhood malignant diseases are staged according to disease-specific staging systems that often differ between countries or clinical trial organisations.[11] The usefulness of population-based registries to childhood cancer research and policy is therefore limited by both the general paucity of cancer stage data, the inadequacy of adult staging systems in showing the extent of disease in children, and the use of many paediatric staging classifications for the same malignant disease. Finally, cancer registries in low-income and middle-income countries face additional challenges in view of the unavailability or unaffordability of advanced imaging.

Our primary objectives were to identify the key principles that should guide the collection of childhood cancer stage by population-based cancer registries, and to recommend which staging system(s) should be used by cancer registries for 18 major childhood malignancies. Staging systems should be able to be applied by registry staff using available records and should be sufficiently detailed for analysis and interpretation of population cancer data, while respecting the different capacities and resources of different registries. The resultant Toronto Paediatric Cancer Stage guidelines have been endorsed by the Union for International Cancer Control TNM Prognostic Factors Project. Our recommendations are not intended to replace staging systems in clinical use.

Methods

We assembled a panel of international experts and advocacy stakeholders, and undertook a modified Delphi approach to build consensus.[12,13] Invited experts represented diverse content skills (eg, clinicians and epidemiologists), geography, and resource settings to ensure the most widely applicable and feasible recommendations.[13] Representatives from selected cancer registries or registry associations were invited, and invitees could nominate additional panellists.

Before starting the Delphi rounds, consensus workshop leaders (Sumit Gupta, A Lindsay Frazier) generated a list of candidate principles informed by the principles that have been endorsed for the collection of cancer stage in adult malignancies by the Union for International Cancer Control TNM Prognostic Factors Project, and through interviews with two experts in cancer registration (Oscar Ramirez, Lynn A G Ries), one from a high-income country and one from a middle-income country.[8] A prior search of Ovid MEDLINE revealed only studies pertaining to specific malignancy cohorts, and we identified no articles that provided

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See Online for appendix

principles for choosing one staging system over another. We then conducted two Delphi rounds by email to gauge consensus on guiding principles relevant to the collection of paediatric cancer stage in population-based registries.

In round one, we asked panellists to score each principle on a 5-point Likert scale.[13] We asked panellists to provide comments on each principle, and to suggest additional principles for inclusion. In accordance with published guidelines, consensus was defined as 75% or more of respondents either agreeing or strongly agreeing with a principle (median score ≤2).[13] Any principle with which 75% or more of respondents disagreed or strongly disagreed with was eliminated.

Next, the consensus workshop leaders reviewed and revised any principles that had not achieved consensus, but had not been eliminated. Based on round one feedback, several entirely new principles were developed. In round two, panellists were asked to score the revised or added principles again, and were provided with their own previous scores from round one, score distribution, and representative comments from the group. Responses were kept anonymous throughout both rounds.

A 1-day in-person meeting was then held for all panellists in Toronto, Canada (Oct 19, 2014). The group reviewed each approved principle for content and phrasing. We discussed those principles that had not achieved consensus and they were subsequently either revised and accepted, or rejected. Finally, all panellists re-reviewed the entire set of principles that had achieved consensus to minimise redundancy.

Panellists then broke into three working groups: haematological malignancies, solid tumours, and neuro-oncology. Each working group was composed of epidemiologists, cancer registrars, and paediatric oncologists with appropriate malignancy expertise. We tasked each group to endorse a staging system for use by population-based cancer registries using the set of principles that had achieved consensus as a guide. Working groups were given a list of the most common paediatric staging systems for each malignancy, but were free to suggest alternatives. Each working group presented their recommendations to the reassembled group, and after incorporating refinements suggested by the reassembled group, made a final recommendation on a staging system. Finally, panellists discussed strategies for disseminating the group's recommendations, expected challenges to adoption, and ways of overcoming these challenges.

Findings

Through an iterative process, two workshop leaders (Sumit Gupta, A Lindsay Frazier) identified 28 panellists who either had expertise in paediatric oncology, epidemiology, cancer registration, or represented a key stakeholder such as the Union for International Cancer Control, International Agency for Research on Cancer, National Cancer Institute, or Surveillance, Epidemiology, and End Results Program (appendix). 26 (93%) experts who accepted the invitation to participate represented 17 countries across six continents. Ten (36%) panellists were from a low-income or middle-income country. Of the 26 experts, 25 (96%) returned responses to the round one survey. All 25 of these respondents returned responses to the round two survey. All 26 participating individuals, plus the two workshop leaders, attended the meeting in Toronto, Canada.

In round one, 18 principles were proposed; 13 achieved consensus and one was eliminated as consensus was not achieved (table 1). The four remaining original principles were modified and one new principle was added according to round one comments, and included in the round two surveys. Of these five second-round principles, three achieved consensus and two did not (table 2). During the workshop, five principles that had achieved consensus were modified to improve phrasing without altering content. Two principles referring to staging systems in low-income and middle-income countries were combined, as were two principles relating to uniformly collecting stage across registries, resulting in a total of 14 core principles.

We grouped principles guiding collection of paediatric stage data into four categories: rationale for collection, relation to adult cancer staging, specificities of paediatric staging systems, and adaptation to resource-limited settings (panel).

Panellists overwhelmingly endorsed the importance of collecting stage for cases of paediatric cancer in population-based registries (table 1). Panellists noted that paediatric age ranges are defined differently across jurisdictions (principle 6).[4,5] We chose not to define an upper age limit for our staging recommendations, because this might vary between malignant diseases. For example, paediatric staging might be appropriate even in adults with neuroblastoma.[14]

Paediatric stage should show the anatomical extent of disease (principle 7),[8] as distinct from the risk of recurrence. For instance, *MYCN* amplification is a crucial prognostic feature in neuroblastoma associated with risk of recurrence, but is not a measure of stage or extent of disease. Non-stage prognostic features might also be collected by registries but should not be confused with stage. Both clinical staging (principle 10) and pathological staging (principle 11) are important. Although pathological staging might allow for more accurate measurement of disease extent through surgical pathology, it could underestimate the initial extent of disease if neoadjuvant therapy has been given. In particular, in paediatric malignant diseases, cooperative groups differ on whether staging before or after neoadjuvant therapy is the most relevant for deciding upon the full course of treatment.[15] The TNM system has prefix modifiers to address this issue. For example, the "y" modifier suggests that the stage of

	Number of responses (n=25)	Percentage agreement*	Median score (IQR)*	Consensus reached
Cancer registries should routinely collect disease stage data for cases of paediatric cancer	25	100%	1 (1–2)	Yes
A primary reason for collecting disease stage in cancer registries is to allow stratified comparison of outcomes between groups or over time	25	96%	2 (1–2)	Yes
A primary reason for collecting disease stage in cancer registries is to identify trends in late presentation through the proxy of advanced stage at diagnosis	25	84%	2 (1–2)	Yes
Stage should reflect the extent of disease	25	96%	1 (1–2)	Yes
Stage data in cancer registries do not need to be as detailed as stage data for the purposes of clinical decision making	25	48%	3 (2–4)	No
Staging systems used in paediatric cancer registries should be as simple yet informative as possible	25	96%	1 (1–2)	Yes
TNM-based staging systems used in adult patients are of limited use for paediatric cases	24	71%	2 (1·75–3)	No
Cancer registries should routinely use paediatric specific staging systems for childhood cancer cases	25	96%	2 (1–2)	Yes
For malignancies common in both paediatric and adult populations (eg, Hodgkin's lymphoma, testicular cancer), staging systems should be the same across both populations	25	80%	2 (1–2)	Yes
Stage should be measured uniformly across all paediatric cancer registries globally to ensure comparability	25	92%	1 (1–2)	Yes
Different paediatric staging systems for the same disease have been developed by different clinical trial organisations; any staging system that is adopted for paediatric cancer registration needs to reconcile these differences	25	76%	2 (1–2)	Yes
When staging paediatric malignancies, clinical staging (ie, staging at the time of diagnosis) is important and should be collected	25	92%	1 (1–2)	No
When staging paediatric malignancies, pathological staging (ie, staging at the time of surgery or resection) is important and should be collected	25	68%	2 (1–3)	No
Clinical and pathological staging classification systems should be identical, and differ only in the timepoint of collection	23	35%	3 (2–4)	No
Cancer registries should collect the methods of evaluation by which stage was determined (eg, diagnostic modalities)	25	56%	2 (1–3)	No
Given significant differences in diagnostic capabilities, staging systems appropriate to settings with limited diagnostic and evaluation capabilities are needed	25	84%	1 (1–2)	Yes
Staging systems designed for resource-limited settings with few diagnostic capabilities should be, when possible, based on collapsing traditional stages used in resource-rich settings, thus preserving a degree of comparability	24	83%	1 (1–2)	Yes
Online tools and algorithms that assign stage based on inputted data (eg, involved sites of disease) are helpful when staging paediatric malignancies†	25	80%	2 (1–2)	Yes

*Agreement was defined as scores of 1 or 2; 1=strongly agree, 2=agree, 3=neither agree nor disagree, 4=disagree, 5=strongly disagree. †This statement achieved consensus, but was removed after the face-to-face meeting as it pertained to dissemination methods and not a core guiding principle.

Table 1: **Results of Delphi round one**

	Number of responses (n=25)	Percentage agreement*	Median score (IQR)*	Consensus reached
TNM-based staging systems used in adult patients are of limited use for many, but not all paediatric malignancies	22	91%	2 (1–2)	Yes
Ideally, cancer registries should collect the methods of evaluation by which stage was determined in order to assess the adequacy of staging (eg, chest x-ray *vs* CT scan for lung metastases)	23	87%	2 (1–2)	Yes
A primary reason for collecting disease stage in cancer registries is because stage may be used as a proxy for treatment	25	52%	2 (2–4)	No
The importance of pathological staging (ie, staging at the time of surgery or resection), and the staging system by which it should be collected, will vary between paediatric malignancies	25	92%	2 (1–2)	Yes
Stage at diagnosis, when collected, should incorporate all information available from diagnosis to 4 months post-diagnosis	25	60%	2 (2–3)	No

*Agreement was defined as scores of 1 or 2; 1=strongly agree, 2=agree, 3=neither agree nor disagree, 4=disagree, 5=strongly disagree.

Table 2: **Results of Delphi round two**

patient disease was assessed after the receipt of neoadjuvant therapy.[16]

Comparability between registries and regions is challenging in the face of several potential barriers. First, registries vary widely in terms of their human, infrastructural, and financial resources. This is of great concern in low-income and middle-income countries. In 2006, only 8% of Asians and 11% of sub-Saharan Africans were covered by population-based cancer registries; when only high-quality registry data are considered, these values are 4% of Asians and 1% of sub-Saharan Africans.[17] This concern is not restricted to low-income and middle-income countries; high-income country registries face increasing funding constraints also.[6] Second, registries vary in their ability to access primary data sources and in data quality. In many jurisdictions, paediatric cancer cases are identified through submission of pathology reports, hospital

Panel: **Toronto Paediatric Cancer Stage principles to guide collection of paediatric cancer stage in population-based cancer registries**

Rationale for collection

Cancer registries should routinely collect disease stage data for cases of paediatric cancer (principle 1)

To allow stratified comparison of outcomes between groups or over time (principle 2)

To identify trends in late presentation through the proxy of advanced stage at diagnosis, though this may not be applicable to all childhood cancers or all jurisdictions (principle 3)

Relation to adult cancer staging

Cancer registries should routinely use paediatric specific staging systems for childhood cancer cases (principle 4)

For malignancies common across paediatric and adult age groups (eg, Hodgkin's lymphoma, testicular cancer), staging systems should be the same (principle 5)

TNM-based staging systems used in adult patients are of limited use for many paediatric malignancies (principle 6)

Specificities of paediatric staging systems

Stage should reflect the extent of disease (principle 7)

Staging systems used in paediatric cancer registries should be as simple yet informative as possible (principle 8)

Registries should collect stage for paediatric cancer according to internationally endorsed classification systems (principle 9)

When staging paediatric malignancies, clinical staging (ie, staging at the time of diagnosis) is important and should be collected (principle 10)

The importance of pathological staging (ie, staging at the time of surgery or resection), and the staging system by which it should be collected, will vary between paediatric malignancies (principle 11)

Adaptation for resource-limited settings

Tiered staging systems should be endorsed, with more detailed systems for well-resourced cancer registries with appropriate data access, and less detailed systems for registries with limited resources and access. Lower-tier systems should be based on collapsing higher-tier system categories to preserve comparability across registries (principle 12)

discharge abstracts, and death certificates.[4,18] By contrast, some jurisdictions have established specialised paediatric registries that benefit from a direct access to clinical records located at each site.[19–21] These models result in a differential ability to access detailed stage data. Although comparability between cancer registries is a key goal,[22,23] a one size fits all approach to the recording of paediatric cancer staging was deemed impractical by panellists.

To balance these two opposing concerns, panellists endorsed a tiered approach to paediatric cancer staging (principle 12). In this tiered approach, lower-tier staging systems are more basic and thus should be feasible for even resource-limited cancer registries to adopt. Higher-tier staging systems are more detailed and comprise several levels that can be collapsed down into those of the lower-tier systems, retaining comparability across registries. Paediatric cancer registries with substantial resources might choose to develop Tier 3 staging systems based on further subdividing Tier 2 categories in ways that continue to have prognostic importance (eg, site of metastases in malignant bone tumours, distinguishing CNS from bone marrow association in non-Hodgkin lymphoma). Comprehensive and valid Tier 1 stage data are preferable to incomplete Tier 2 data of unknown quality, and would still represent a major improvement in many jurisdictions.

The panel did not reach consensus on one principle during the face-to-face meeting, although it engendered much discussion. Stage is partly representative of the diagnostic modalities used to ascertain it. Access to these modalities will vary widely between or within international jurisdictions. For example, the staging work-up for Burkitt's lymphoma might range from clinical exam with or without ultrasonography in resource-limited centres to combined CT/PET scans in many centres in high-income countries.[24,25] Children identified with high-stage disease in these two settings might not be comparable; knowing which diagnostic modalities were used would allow assessment of staging adequacy when attempting cross-registry comparisons. These data would allow for changes in stage distribution to be identified as diagnostic capabilities improve.[26] We discussed the notion of collecting data on the validity of stage with the accepted approach of recording the means of diagnosis (clinical, histological, etc) via a so-called certainty, or c-factor, already included as a concept of cancer registration.[27] Despite strong consensus on the utility of such information, panellists noted the difficulty in collecting this data and the resources needed. Although concerns over practicality prevented full group endorsement as a core principle, there was enthusiasm for pilot studies to establish the feasibility of collecting stage assessment methods and whether the c-factor notion could be applied to cancer stage data.

Working groups were encouraged to endorse malignancy-specific tiered staging systems when appropriate to help to strike a balance between what staging information would ideally be recorded, with the practical implications of obtaining such information.

We provide recommendations for the collection of stage for the major childhood cancers (table 3). Working groups noted that tumour stage is just one component of prognostic risk classification. Although we restricted the purview of this meeting to stage, or extent of disease, other prognosticators could be considered for collection by registries with adequate resources and data access (eg, cytogenetics in acute leukaemia, *MYCN* status in neuroblastoma, molecular or epigenetic characterisations in brain tumours, International Germ Cell Consensus Classification for metastatic germ-cell tumours, extent of surgical resection in CNS tumours).

	Tier 1 staging system	Tier 2 staging system	Comments
Acute lymphoblastic leukaemia	CNS negative	CNS 1[28]	Collection of testicular involvement not endorsed given rarity and uncertain prognostic value in first presentation disease; white blood cell count at presentation was not considered reflective of stage
	CNS positive	CNS 2	
	CNS positive	CNS 3	
Acute myeloid leukaemia	CNS negative	CNS negative[29]	..
	CNS positive	CNS positive	
Chronic myeloid leukaemia	None	None	No relevant staging system identified or necessary
Hodgkin's lymphoma	Ann Arbor—stage IA/B[30] Ann Arbor—stage IIA/B Ann Arbor—stage IIIA/B Ann Arbor—stage IVA/B	Ann Arbor—stage IA/B[30] Ann Arbor—stage IIA/B Ann Arbor—stage IIIA/B Ann Arbor—stage IVA/B	Used in both adult and paediatric populations; recent proposals in adult populations to move to more simplified limited *vs* advanced staging classifications[31] not yet evaluated in paediatric populations; multi-tiered staging systems deemed not appropriate
Non-Hodgkin lymphoma	Limited	St Jude/Murphy—stage I[32]	Tier 1 advanced stage indicates CNS or bone marrow involvement; although some clinicians will use Ann Arbor staging for non-Hodgkin lymphoma, St Jude/Murphy more often used in paediatric populations; Ann Arbor stage IV will often correspond to Tier 1 advanced stage disease; whether Ann Arbor or St Jude/Murphy staging systems were used by clinicians can be difficult to ascertain from medical charts
	Limited	St Jude/Murphy—stage II	
	Limited	St Jude/Murphy—stage III	
	Advanced	St Jude/Murphy—stage IV	
Neuroblastoma	Localised	INRGSS—localised L1[33]	MS disease refers to children younger than 18 months with metastases confined to skin, liver, or bone marrow; the first two stages of the Tier 1 system are intended to be simplified proxies of INRGSS L1 and L2 not dependent on adequate assessment of imaging-defined risk factors
	Locoregional	INRGSS—locoregional L2	
	Metastatic	INRGSS—metastatic M	
	INRGSS—MS disease	INRGSS—MS disease	
Wilms' tumour	Localised	Stage I[15]/y-stage I[15]	y designates that staging assessment was performed after neoadjuvant therapy was given, which allows the staging system to accommodate both SIOP and COG/NWTSG-based treatment strategies;[15] in cases of bilateral disease the stage of the most advanced kidney should be recorded
	Localised	Stage II/y-stage II	
	Localised	Stage III/y-stage III	
	Metastatic	Stage IV	
Rhabdomyosarcoma	Localised	TNM stage 1[27]	Rhabdomyosarcoma overall stage incorporates both TNM staging and site of disease; as registries collect primary disease site, overall rhabdomyosarcoma stage may be approximated with either tier staging system; for very high-resourced registries, a Tier 3 system that incorporates site of metastases could be considered
	Localised	TNM stage 2	
	Localised	TNM stage 3	
	Metastatic	TNM stage 4	
Non-rhabdomyosarcoma soft-tissue sarcomas	Localised	TNM stage 1[27]	..
	Localised	TNM stage 2	
	Localised	TNM stage 3	
	Metastatic	TNM stage 4	
Osteosarcoma	Localised	Localised	Although more detailed staging systems exist,[34] their clinical and prognostic value is limited; multi-tiered staging systems were not deemed appropriate; for very high-resourced registries, a Tier 3 system which incorporates site of metastases could be considered
	Metastatic	Metastatic	
Ewing's sarcoma	Localised	Localised	Although more detailed staging systems exist,[34] their clinical and prognostic value is limited; multi-tiered staging systems were not deemed appropriate; for very highly resourced registries, a Tier 3 system incorporating site of metastases may be considered
	Metastatic	Metastatic	

(Table 3 continues on next page)

	Tier 1 staging system	Tier 2 staging system	Comments
(Continued from previous page)			
Retinoblastoma	Localised (intraocular)	IRSS stage 0[35]	In keeping with current registry guidelines for retinoblastoma, in cases of bilateral disease the stage of the most advanced eye should be recorded; within IRSS stage 0, group A–E was considered Tier 3 recommendation
	Localised (intraocular)	IRSS stage I	
	Localised (intraocular)	IRSS stage II	
	Regional (orbital or regional lymph nodes)	IRSS stage III	
	Distant (extra-orbital)	IRSS stage IV	
Hepatoblastoma	Localised	Localised	Collection of PRETEXT is a Tier 3 option[36]
	Metastatic	Metastatic	
Testicular	Localised	TNM stage I[37]	Although the Tier 1 and Tier 2 staging systems correlate perfectly, the individual components of TNM staging would not be collected in the Tier 1 system
	Regional	TNM stage II	
	Metastatic	TNM stage III	
Ovarian	Localised	FIGO stage I[38]	..
	Regional	FIGO stage II	
	Regional	FIGO stage III	
	Metastatic	FIGO stage IV	
Astrocytomas	None	None	No relevant staging system identified or necessary
Medulloblastoma and other CNS embryonal tumours	M0 or localised	M0[11]	Residual disease, defined as >1·5 cm² after resection, is an important non-stage prognostic factor and could be considered for collection by appropriately resourced registries[39,40]
	M+ or metastatic	M1	
	M+ or metastatic	M2	
	M+ or metastatic	M3	
	M+ or metastatic	M4	
Ependymoma	M0	M0	Extent of resection, defined as no resection *vs* subtotal *vs* gross total, is an important non-stage prognostic factor and might be considered for collection by appropriately resourced registries
	M+	M1	
	M+	M2	
	M+	M3	
	M+	M4	

Tiered staging systems for the main childhood cancers. AJCC=American Joint Committee on Cancer. COG=Children's Oncology Group. FIGO=International Federation of Gynaecological Oncologists. INRGSS=International Neuroblastoma Risk Group Staging System. IRSS=International Retinoblastoma Staging System. NWTSG=National Wilms Tumour Study Group. SIOP=International Society of Paediatric Oncology.

Table 3: **The Toronto Paediatric Cancer Stage guidelines**

Discussion

Haematological malignancies

Although the idea of cancer stage is not traditionally applied in acute leukaemia, the extent of CNS involvement has been shown to have clear prognostic importance, particularly in acute lymphoblastic leukaemia.[28,29] Therefore, standard classifications of CNS involvement are endorsed for both acute lymphoblastic leukaemia and acute myeloid leukaemia. Prognostic information unrelated to the extent of disease, such as white blood cell count and immunophenotype, are crucial for patient management, but fall outside the scope of this Review. No staging system is endorsed for chronic myeloid leukaemia.

The Ann Arbor staging system is well accepted in both paediatric and adult Hodgkin's lymphoma and is therefore recommended.[30] Although Ann Arbor staging is usually used in adults with non-Hodgkin lymphoma, its usefulness in paediatric non-Hodgkin lymphoma is more limited because it is unable to adequately describe the extent of extra-nodal association.[41] In the most common paediatric non-Hodgkin lymphomas (eg, Burkitt's lymphoma, anaplastic large-cell lymphoma), extra-nodal disease is common, with only CNS or bone marrow involvement having substantial prognostic effect.[42] The Ann Arbor staging system does therefore not allow the proper stratified comparison of outcomes between groups (principle 2). The Lugano classification was likewise not endorsed because of its focus on adult lymphomas.[43] The St Jude/Murphy system, which records the extent of extra-nodal

involvement, is generally preferred in paediatric non-Hodgkin lymphoma and was therefore endorsed instead.[32]

A new International Paediatric Non-Hodgkin Lymphoma Staging System has been proposed, building upon the St Jude/Murphy system.[44] Because the Paediatric Non-Hodgkin Lymphoma Staging System is not used in paediatric protocols and awaits prospective validation, we did not incorporate it into our recommendations. Because staging systems evolve over time, future iterations of these recommendations could well include the Paediatric Non-Hodgkin Lymphoma Staging System.

Solid tumours

In general, for solid tumours, a simplified classification describing extent of disease (eg, localised, regional, or metastatic) should be used for Tier 1 staging systems (table 3).

For neuroblastoma, the International Neuroblastoma Risk Group Staging System should be used for both tiers.[33] The International Neuroblastoma Risk Group Staging System was developed to be able to compare preoperative extent of disease independent of surgical skill and availability to overcome this specific criticism of the predecessor staging system, the International Neuroblastoma Staging System.[33] The International Neuroblastoma Risk Group Staging System recognises that resectability partly suggests extent of disease but is also defined by the location and invasion of the tumour. These features, such as aorta encasement or tracheal compression, can be established by preoperative imaging (image-defined risk factors). An International Neuroblastoma Risk Group Staging System L1 tumour is defined as a localised tumour not involving a vital structure as defined by the list of image-defined risk factors and confined to one compartment. International Neuroblastoma Risk Group Staging System L2 tumours are defined as locoregional tumours with the presence of one of more image-defined risk factors. Although low-resource settings might not be able to obtain cross-sectional imaging that would allow assessment of all image-defined risk factors, clinicians usually decide, based on the data available, whether the patient is L1 or L2. The MS stage of International Neuroblastoma Risk Group Staging System staging is analagous to the stage IV–S of the International Neuroblastoma Staging System in which children less than 18 months of age with metastases confined to skin, liver, and bone marrow have an excellent outlook and are classified separately to prevent over-treatment. By contrast, children less than 18 months of age with bone metastases are classified as stage M (or stage IV disease in the International Neuroblastoma Staging System system), and have a worse prognosis that merits more intensive therapy.

For Wilms' tumour, two major staging systems exist. The Children's Oncology Group/National Wilms Tumor Study Group staging system is based on postoperative, pre-chemotherapy pathological features and findings; the International Society of Paediatric Oncology (SIOP) stage is based on the findings at surgery after the patient has received neo-adjuvant chemotherapy.[15] This practice pattern is unlikely to change. For this malignancy, therefore, the use of the TNM y prefix should be adopted for staging of the abdominal tumour. The y prefix denotes the fact that stage was identified after neoadjuvant chemotherapy was given: for example, a y-stage II would be equivalent to a SIOP stage II. Both groups recognise the presence of metastatic (stage IV) disease at diagnosis, based on imaging findings. Efforts to encourage institutions and cooperative trial groups to collect data based on preoperative imaging irrespective of what staging system was used to identify treatment would be welcome, but were beyond the scope of the panel.

In rhabdomyosarcoma, several factors establish appropriate treatment,[45] including the classic components of TNM staging: the size of the tumour (less or more than 5 cm), the presence of nodal metastases, and metastatic disease. However, some anatomical sites have a more favourable prognosis than others. The panel noted that tumour site is already routinely recorded in cancer registries as part of International Classification of Disease-O coding, thus obviating the need to explicitly incorporate favourable versus unfavourable site into registry staging systems. Likewise, histology (embryonal *vs* alveolar) is prognostic, but is routinely collected as part of registry procedures. Finally, clinical group, describing the extent of resection, is also used to identify treatment. Given the dependence on the availability and skill of the surgeon, the collection of group data for rhabdomyosarcoma is not recommended for general registry uses. In bone tumours, only two stages are recognised (localised or metastatic) for both Tier 1 and Tier 2 systems.

In many patients with solid tumours, site of metastasis might offer additional information on risk, with non-lung metastases (eg, bone, bone marrow) portending worse outcomes than lung metastases. Although the panel felt that site of metastasis represented a level of detail whose collection was beyond the capabilities of most population-based cancer registries, this variable could ideally be recorded by high-resourced registries as part of a Tier 3 system.

For retinoblastoma, the key prognostic criteria is whether the disease remains localised within the eye, has spread regionally (orbital or regional lymph nodes), or has spread to metastatic sites. The International Retinoblastoma Staging Systems captures this progression in the extent of disease by including a stage 0 in which enucleation was not needed and ocular preservation treatments are applied. However, in high-income countries, the disease is typically detected at an early stage and hence treatment success is measured in terms of salvage of the eye itself, or the globe. Grouping systems have been developed that assess the extent of intraocular

disease and thus the likelihood of eye salvage, beginning with the Reese-Ellsworth system. Intraocular staging might be considered as an additional variable to be collected by registries with sufficient resources.[35]

For liver tumours, in resource-limited settings, the classification of the tumour as either localised or metastatic is sufficient. Liver tumours in high-income countries are increasingly staged with SIOP pre-treatment systems (PRETEXT) based on the number of liver segments implicated.[36] PRETEXT staging includes a designation of E, for extrahepatic disease, which is synonymous with regional extension of the tumour and a designation for association with the portal (P) or hepatic (H) veins. However, there is much variability in PRETEXT assignations between observers when local institutional assignments have been compared with central expert review. Therefore, the collection of PRETEXT could be deemed a Tier 3 variable, but the presence or absence of metastatic disease would be sufficient in both Tiers 1 and 2.

The most common tumours of the testes and ovary in paediatrics are germ-cell tumours. Because testicular tumours are most prevalent in young adults, the standard method of assigning stage, the TNM criteria, should be used.[37] For patients with disease that has spread beyond the testicle to the nodes or more distant metastatic sites, International Germ Cell Consensus Classification (IGCCC) is used to assign risk group and recommend therapy.[46] The IGCCC incorporates the levels of postoperative tumour markers into the classification. In high-resource settings, registries could therefore deem the collection of both site of metastatic disease and postoperative tumour marker levels as important non-stage prognostic variables.

For ovarian germ-cell tumours, which occur mostly in older adolescents and young adults, the most common staging system used is the International Federation of Gynecology and Obstetrics (FIGO) classification.[38] The FIGO system was developed mainly for epithelial ovarian cancer and might not be wholly relevant for ovarian germ-cell tumours, but to be consistent with the data collected in adult women, recording FIGO stage is recommended.

CNS tumours

Astrocytic tumours, medulloblastoma, and ependymoma account for about 80% of all paediatric CNS tumours. Extent of disease is an important prognostic factor in determining the intensity of therapy and predicting the outcome for many CNS malignancies, including medulloblastoma, other embryonal CNS tumours (pineoblastoma, primitive neuroectodermal tumour, atypical teratoid rhabdoid tumour), and ependymomas.[47] Extent of disease is classified according to the M stage. In the absence of visible disease beyond the primary on imaging (MRI brain and spine) and absence of malignant cells in the cerebrospinal fluid), M0 applies. M1 codes positive tumour cells in the cerebrospinal fluid, M2 visible metastases in brain, M3 visible metastases in spine, and M4 metastases outside of the CNS.[11]

Prognosticators in childhood astrocytomas include histology, WHO grade, and site of disease. Astrocytomas are unlikely to spread beyond their initial site; examination of the cerebrospinal fluid is not deemed necessary in the initial work-up. The working group therefore endorses no staging system for these malignancies.

Although extent of surgical resection in CNS tumours has crucial prognostic effect, it does not show anatomical extent of disease and should therefore be deemed a non-stage prognostic factor. Extent of resection is classified as no resection (including biopsy) versus subtotal versus gross total resection for astrocytic tumours and ependymomas. In medulloblastoma, the extent of resection is classified according to the amount of residual disease.[39,40]

Barriers to adoption

There are several barriers to the widespread adoption of these staging recommendations by population-based cancer registries. Childhood cancer represents a small percentage of the overall cancer burden in a population.[10,48] General population-based cancer registries therefore focus their efforts on collecting data on major neoplasms that occur in adults and might not have sufficient time and energy to refine classifications aimed at this small sub-population. Advocacy efforts on the part of childhood cancer organisations could be needed to overcome this barrier.

Additionally, many registries face limited and even decreasing funding.[6] To capture any additional data elements will require increased resources. Registries initiating the capture of paediatric cancer stage should identify the amount of additional funding needed to do so to better inform health policy makers and researchers in other jurisdictions. Studies using stage data (eg, outcome comparisons between groups or over time, trends in disease extent at presentation) will help to show the utility of collection of these data to advocates, policy makers, and clinicians. Here, the rarity of childhood cancer might be an advantage; a small outlay of additional funds to collect stage in paediatric patients, then an establishment of the feasibility and value of stage data, will help advocate for similar efforts in adult populations.

For registries that already collect paediatric stage, there might be resistance to changing practice and implementing our guidelines. This could be particularly difficult in countries without a national registry but with many subnational registries. However, there are substantial benefits of a uniform system that can be used by registry staff with available records and that will allow consistent reporting and international comparisons.

Registries are limited by what data are available in medical records. Additional efforts are needed to ensure that clinicians clearly and consistently document cancer stage in sources accessible to cancer registrars.

Search strategy and selection criteria

To generate candidate principles that would guide the collection of childhood cancer stage by population-based cancer registries, Ovid MEDLINE was searched using the exploded terms: "neoplasms/" AND "registries/" AND "neoplasm staging/" AND "child/". The search was limited to articles in English and published from Jan, 1990, to March, 2014. The 236 identified articles pertained to specific cohorts with particular malignancies and not candidate principles.

Limitations

We used a modified Delphi approach to achieve our objectives. A limitation of this approach is its dependence on the composition of the participant group—"homogeneity in Consensus Group composition is likely to result in homogeneity of ratings".[13] Homogeneity increases the likelihood of specific biases affecting the recommendations. We addressed these limitations by ensuring a wide range of viewpoints in the consensus group, including both clinicians and epidemiologists, panellists from countries of all levels of income, geographic diversity, experts in paediatric and adult cancer staging, individuals with experience of leading cancer registries, and representatives of major international stakeholder organisations. This heterogeneity of backgrounds lends credibility to the recommendations endorsed by group consensus. Lending further credibility, our guidelines have subsequently been endorsed by the Union for International Cancer Control TNM Prognostic Factors Project.

Conclusion

Stage is essential for the determination of cancer prognosis, and therefore warrants collection by population-based cancer registries. Because most paediatric cancers have specific staging systems, general adult stage classifications are not appropriate. We recommend that the tiered, paediatric-specific staging systems endorsed in this Review as the Toronto Paediatric Cancer Stage guidelines be adopted for paediatric cases by cancer registries in countries of all income levels, and integrated into registry manuals. To help with this, coding guidelines will be disseminated through various platforms, including various stakeholder organisations. Pilot investigations that determine how the methods used to record stage affect the quality of the data and the resources needed to collect valid paediatric stage data across various resource settings will help inform policy makers. Such pilot studies are already underway in Australia and several Central American jurisdictions. The results of these pilot investigations, implementation experience from other registries, and future changes in treatment and progress, will probably require future modifications to these endorsements, an iterative process characteristic of all staging systems. Finally, comparative studies across jurisdictions and time will help show the value of population-based stage data.

Contributors

SG and ALF conceived of the study idea and design. SG did the analyses. All authors were involved in the data interpretation and crucial revisions of the report, and approved the final version. SG is the guarantor of the report, had full access to all the data, and had final responsibility for the decision to submit for publication.

Declaration of interests

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