Implementing The Toronto Childhood Cancer Staging Guidelines

Lindsay Frazier MD ScM
Kentucky Cancer Registry Annual Meeting
Thursday, November 18, 2021

Investigator Team

Dr. Sumit Gupta
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Prof Joanne Aitken
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International Assoc.
of Cancer Registries.
Lead, Australian
Childhood Cancer
Registry

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Today's Agenda

| Discussion Focus: |
| :---: |
| *Background, Key Questions, & Objectives* |
| *Toronto Guidelines In Practice* |
| *Assessment of Toronto Guidelines & Next Steps* |

Discussion Focus:

Background, Key Questions, & Objectives

Putting Toronto Guidelines In Practice

Assessment of Toronto Guidelines & Next Steps

Dominican Republic

Neuroblastoma in AHOPCA 2000-2010
[n=183]

Soad Fuentes, MD
El Salvador
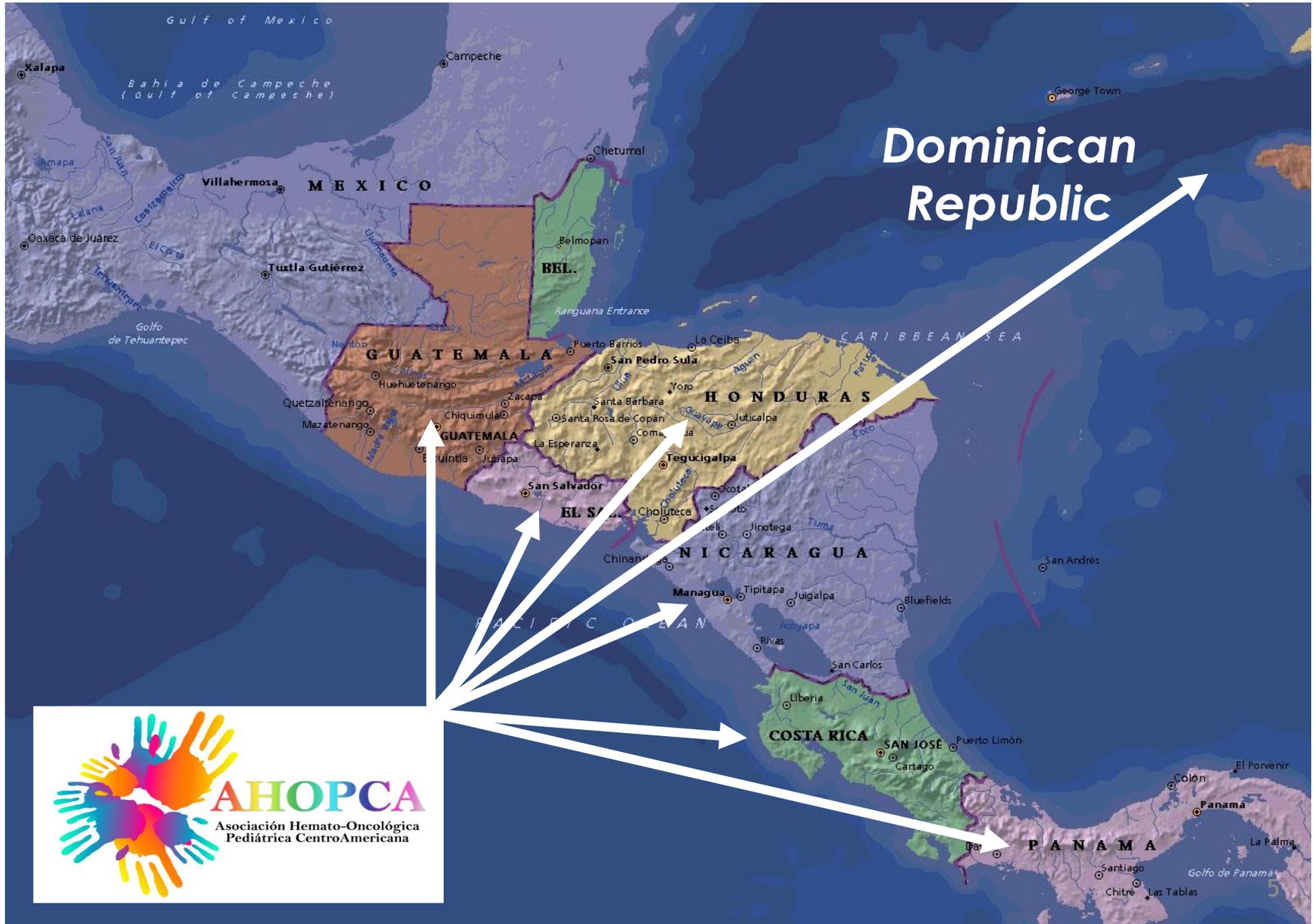
Neuroblastoma in AHOPCA 2000-2010
[n=183]

COUNTRY	Number of Cases per Year	Population <15 y	Estimated Incidence per Million
Guatemala	3	5267120	0.6:1000000
El Salvador	3	1857962	1.6:1000000
Honduras	2	2988687	0.7:1000000
Nicaragua	3	2,412,060	1.2:1000000
Costa Rica	2	1125834	1.8:1000000
Panama	1	989692	1.0:1000000
Dominican Republic	3	2937211	1.0:1000000

U.S.A: 8-9:1 000 000

Soad Fuentes, MD
El Salvador

Parkin DM. Nat Rev Cancer 2006

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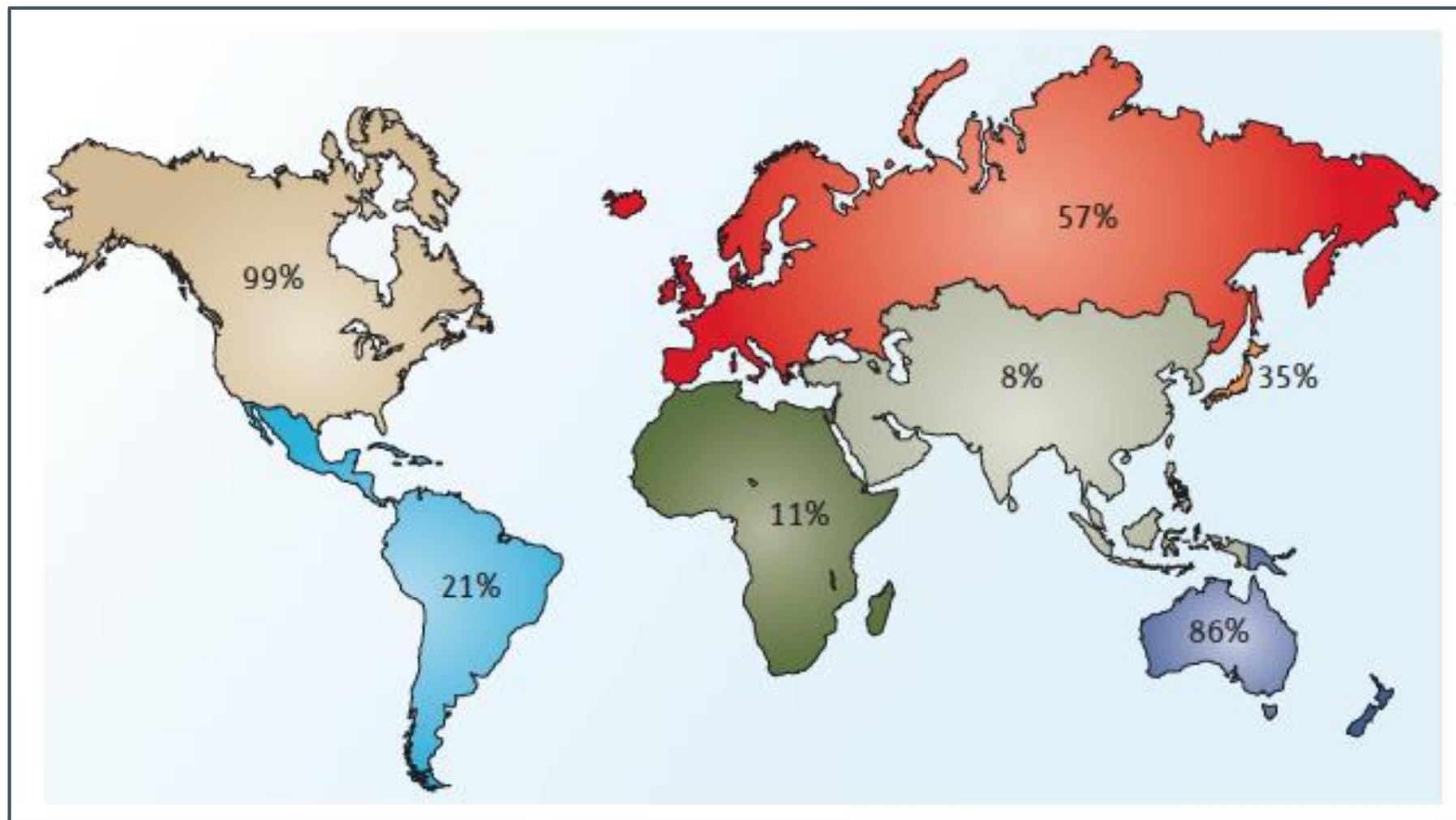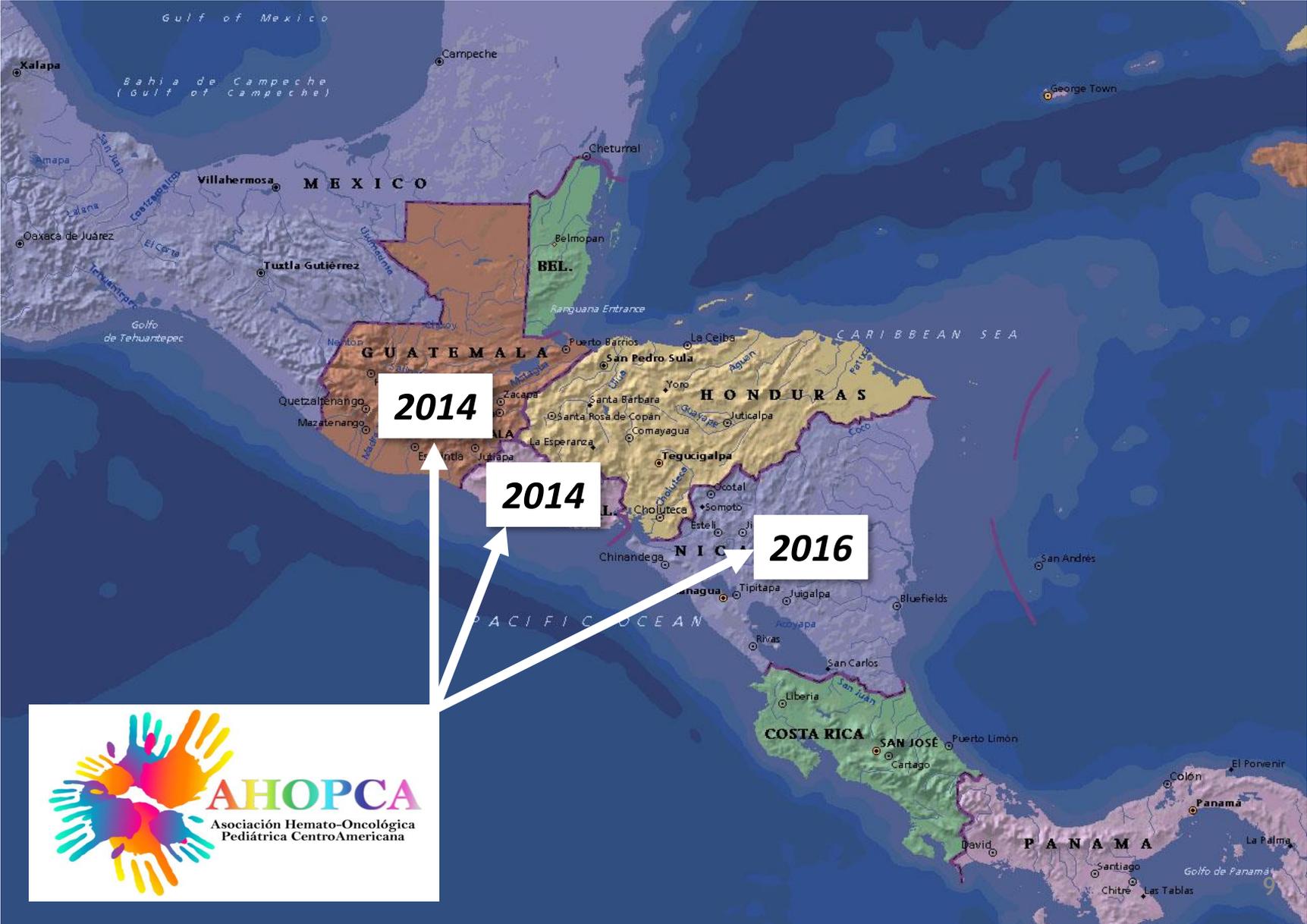
Epiphany: Cancer Registries Don't Collect Stage!

- Many/most population-based cancer registries (PBCRs) ***do not collect stage in adults***

- And cancer registries are even ***less likely to collect pediatric stage*** because childhood cancer already ***poses a data management challenge*** for PBCRs (rarity, heterogeneity)

- Unclear which staging system to use?
  - Many/most childhood cancers are ***not staged with TNM***
  - Additionally, there is more than one system:
    - National childhood clinical trial organization in ***US and Europe have developed their own systems***
    - Thus, there are ***multiple childhood staging systems for the same malignancy***

Why not just use TNM? Only use for STS in practice

Included in TNM
Bone Sarcoma
Soft Tissue Sarcoma *Rhabdomyosarcoma
Ovarian Tumor
Testis Tumor
Retinoblastoma
Hodgkin's Lymphoma
Non-Hodgkin's Lymphoma

Not included in TNM
Acute Lymphoblastic Leukemia
Neuroblastoma
Nephroblastoma (Wilms)
Hepatoblastoma
Astrocytoma
Medulloblatoma
Ependymoma

Why not just use SEER?

- As mentioned, pediatric oncologists have developed "bespoke" staging systems that we all use and are the way we communicate with each other.
- Needed an international solution
- Not clear what "regional" really means

Code	Definition
0	In situ
1	Localized only
2	Regional by direct extension only
3	Regional lymph nodes only
4	Regional by BOTH direct extension AND lymph node involvement
7	Distant site(s)/node(s) involved
8	Benign/borderline*
9	Unknown if extension or metastasis (unstaged, unknown, or unspecified) Death certificate only case

Why is <u>pediatric</u> cancer stage <u>so important</u> for PBCRs?

- ***For adult cancers, incidence is a key cancer control metric.***
  - Can decrease incidence through:
    - Risk reduction (tobacco prevention/cessation, obesity reduction, etc)
    - Screening (Pap, mammogram, colonoscopy, etc).
  - <u>Reducing incidence will reduce mortality</u>.

- ***For pediatric cancer, <u>stage at diagnosis, not incidence,</u> is a key cancer control metric.***
- ***Why?***
  - We cannot decrease incidence (no risk reduction, no screening)
  - <u>Diagnosing children at an earlier stage will improve survival</u>

To Create a Consensus Recommendation, We Assembled a Panel of Experts From Across the Globe

*Key stakeholders held diverse expertise, including **pediatric oncology, cancer registration, and cancer epidemiology***

Childhood Cancer Stage Collection: Results

Characteristics of Consensus Group Participants (n=28)

	N (%)
Gender	
Male	12 (42·9)
Female	16 (57·1)
Geographic area	
Canada/USA	12 (42·9)
Europe	5 (17·9)
Asia	5 (17·9)
Latin America	4 (14·3)
Africa	1 (3·6)
Oceania	1 (3·6)
Resource setting*	
HIC	18 (64·3)
LMIC	10 (35·7)
Area of expertise**	
Clinical paediatric oncology	20 (71·4)
Epidemiology	14 (50·0)
Cancer registration	15 (53·6)

Meeting Attendees

Childhood Cancer Stage Collection: Objectives

1. To ***identify the key principles*** that should guide the collection of childhood cancer stage by PBCRs

2. Using these principles, ***recommend which staging system(s) should be used by PBCRs*** for 18 major childhood cancers

3. Do so ***respecting different capacities and resource levels*** in high income vs. low-middle income countries

Note: NOT intended to replace current clinical practice or to replace what is possible in HBCR; ONLY for the purpose of PBCR data collection.

Modified Delphi Approach to Consensus Building

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Childhood Cancer Stage Collection: Methods

| Delphi Round 1 [April 2014] | Delphi Round 2 [June 2014] | Face-to-Face Meeting: SIOP Toronto [October 2014] |

- ✓ Email surveys of key stakeholders to get input & agreement of the principles of staging

- ✓ Final agreement on principles
- ✓ Working groups created for heme malignancy, solid tumors and neuro-onc
- ✓ Each working group tasked with endorsing staging system for pediatric cancers in their "realm"
- ✓ Recommendations presented to reassembled full group

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Rationale for Collection
1. Cancer registries should routinely collect disease stage data for cases of paediatric cancer.
2. A primary reason for collecting disease stage in cancer registries is to allow stratified comparison of outcomes between groups or over time.
3. 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.
Relationship to Adult Cancer Staging
4. Cancer registries should routinely use paediatric specific staging systems for childhood cancer cases.
5. For malignancies common across both paediatric and adult age groups (e.g. Hodgkin lymphoma, testicular cancer), staging systems should be the same.
6. TNM based staging systems used in adult patients are of limited use for many, but not all paediatric malignancies.
Specificities of Paediatric Staging Systems
7. Stage should reflect the extent of disease.
8. Staging systems used in paediatric cancer registries should be as simple yet informative as possible.
9. Registries should collect stage for paediatric cancer according to internationally endorsed classification systems.
10. When staging paediatric malignancies, clinical staging (i.e. staging at the time of diagnosis) is important and often should be collected.
11. The importance of pathologic staging (i.e. staging at the time of surgery/resection), and the staging system by which it should be collected, will vary between paediatric malignancies.
Adaptation for Resource-Limited Settings
12. "Tiered"-staging 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 more limited resources and access. Lower-tier systems should be based on collapsing higher-tier system categories in order to preserve a degree of comparability across registries.

Toronto Childhood Stage Guidelines:
Tiered Staging Systems

Rationale for Collection
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- ***Large variability between PBCRs*** worldwide in terms of human, infrastructural and financial resources

- Variability in ***access to primary data sources***

- Need to ***maintain comparability between PBCRs*** while recognizing and accounting for this variability

- <u>Tiered approach:</u>

  - ***Lower tier staging systems*** are more basic, and thus more feasible for even resource-limited PBCRs

  - ***Higher tier systems*** are more detailed; levels can be collapsed down into those of lower-tier systems

  - Complete and valid ***Tier 1 stage data preferable to incomplete Tier 2 data***

Example of Endorsed Systems:
Wilms Tumor

Malignancy	Tier 1 Staging System	Tier 2 Staging System
Wilms tumour	Localized	Stage I[18] / y-Stage I[18]
		Stage II / y-Stage II
		Stage III / y-Stage III
	Metastatic	Stage IV

- The treatment of Wilms Tumor *varies dramatically by region:* in the US, COG recommends upfront resection followed by chemotherapy while in Europe, SIOP recommends chemotherapy (neo-adjuvant) prior to surgery
  - Thus, *stage is determined at different points in treatment*: a COG stage I patient is not the same as a SIOP stage I patient
  - Using the nomenclature endorsed by TNM committee, a "y" designates that staging assessment was performed after neo-adjuvant therapy was given

Thus *both COG and SIOP based treatment strategies –and hence staging systems--could be accommodated*

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Review

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

Sumit Gupta, Joanne F Aitken, Ute Bartels, James Brierley, Mae Dolendo, Paola Friedrich, Soad Fuentes-Alabi, Claudia P Garrido, Gemma Gatta, Mary Gospodarowicz, Thomas Gross, Scott C Howard, Elizabeth Molyneux, Florencia Moreno, Jason D Pole, Kathy Pritchard-Jones, Oscar Ramirez, Lynn A G Ries, Carlos Rodriguez-Galindo, Hee Young Shin, Eva Steliarova-Foucher, Lillian Sung, Eddy Supriyadi, Rajaraman Swaminathan, Julie Torode, Tushar Vora, Tezer Kutluk, A Lindsay Frazier

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The Guidelines were in 8th Edition of TNM. There is, <u>for the first time</u>, a chapter on childhood cancers.
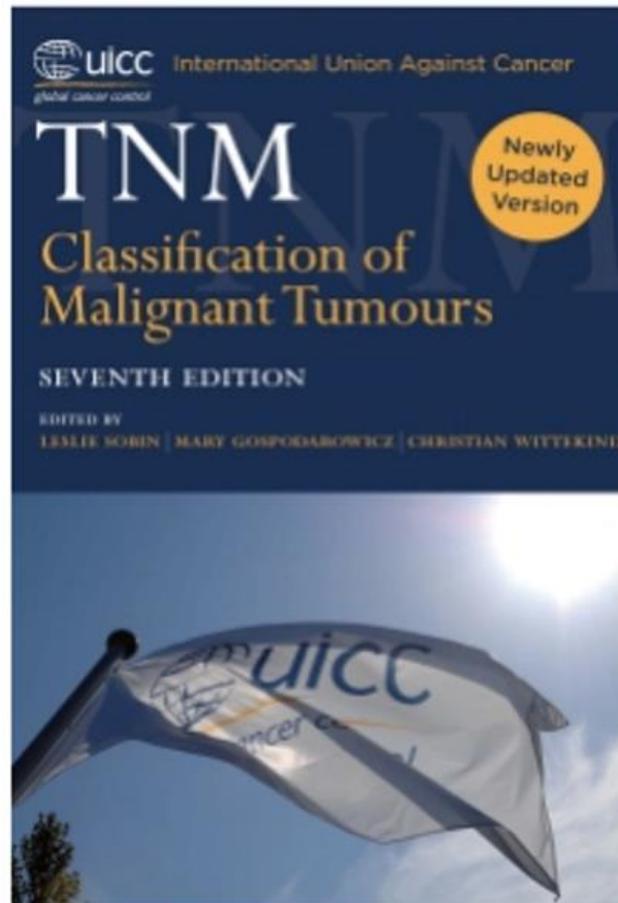
TNM Classification of Malignant Tumours - 8th edition

Changes between the 7th and 8th editions

January 2018

"We unite the cancer community to reduce the global cancer burden, to promote greater equity, and to integrate cancer control into the world health and development agenda."

Paediatric Tumours

- A consensus meeting held in 2014 recommended a tiered staging system with more detailed systems for well-resourced cancer registries and less detailed systems for registries with limited recourses and access

- The recommendations for tier 1 and 2 follow are published the the 8th edition TNM Classification of Malignant Tumours

- For some cancers recommendations are the same as described earlier for adult patients

Development of paediatric non-stage prognosticator guidelines for population-based cancer registries and updates to the 2014 Toronto Paediatric Cancer Stage Guidelines

Sumit Gupta*, Joanne Aitken*, Ute Bartels, Nickhill Bhakta, Mihaela Bucurenci, James D Brierley, Beatriz De Camargo, Eric Chokunonga, Jessica Clymer, Dana Coza, Chris Fraser, Soad Fuentes-Alabi, Gemma Gatta, Thomas Gross, Zsuzsanna Jakab, Betsy Kohler, Tezer Kutluk, Florencia Moreno, Kayo Nakata, Sari Nur, D M Parkin, Lynne Penberthy, Jason Pole, Jenny N Poynter, Kathy Pritchard-Jones, Oscar Ramirez, Lorna Renner, Eva Steliarova-Foucher, Michael Sullivan, Rajaraman Swaminathan, Liesbet Van Eycken, Tushar Vora, A L Frazier

Panel: **Guiding principles of the collection of non-stage prognosticators of childhood malignancies in population-based registries**

Rationale for collection
1) Cancer registries should collect data on NSPs for cases of paediatric cancer when appropriate
2) A primary reason for collecting NSPs in registries, in addition to Toronto Stage, is to allow for the stratified comparison of outcomes between groups or over time
3) An additional reason for collecting NSPs in registries is to enhance the ability to conduct aetiological and epidemiological studies
4) An additional reason for collecting NSPs in registries with the ability to link to treatment data is to assess concordance with treatment guidelines

Collection of NSPs
5) Not all NSPs should be collected by registries
6) The methods to measure the NSP must be standardised and reproducible
7) Within the relevant jurisdiction and health system, testing for the NSP should ideally be widely available
8) NSPs collected by registries should be considered essential to clinical practice for either decision making or prognostication
9) For cancers where multiple NSPs are highly correlated, registries should only collect one of the correlated NSPs
10) For cancers with many NSPs, a small set should be prioritised for collection by registries
11) Prioritisation of which NSPs to collect should be on the basis of the following:
a) prognostic impact; b) feasibility; c) availability, and; d) registry purpose

NSP=non-stage prognosticator.

	Essential	Additional	New and promising	Comments
Haematological malignancies				
Acute lymphoblastic leukaemia	Age, initial white blood cell count, and lineage	Cytogenetics	..	Lineage can be divided into precursor B cell versus precursor T cell (with the use of ICD-O-3* categories); cytogenetic categories are defined according to the ICD-O-3 classification; and minimal residual disease is not considered (response to therapy)
Acute myeloid leukaemia	..	Cytogenetics	..	Cytogenetic categories are defined according to the ICD-O-3 classification (the most relevant are discussed in the main text); and minimal residual disease is not considered (response to therapy)
Chronic myeloid leukaemia	..	..	..	..
Hodgkin lymphoma	..	..	..	..
Non-Hodgkin lymphoma	Histology	..	..	The most common subtypes in children have unique ICD-O-3 codes
Solid tumours				
Neuroblastoma	..	N-myc	..	..
Wilms tumour	Histology	..	Specific aberrations on chromosomes 1p, 16q, or 1q	Histological sub-classification will depend on if assessed before or after adjuvant chemotherapy; see main text for details
Rhabdomyosarcoma	Histology; anatomical location	Cytogenetics	..	Histological categories based on ICD-O-3 classification; and anatomical location captured through ICD-O-3 topography codes
Non-rhabdomyosarcoma soft tissue sarcomas	..	..	..	..
Osteosarcoma	..	..	..	..
Ewing sarcoma	..	..	..	..
Retinoblastoma	..	..	..	..
Hepatoblastoma	..	..	..	..
Testicular	..	..	..	..
Ovarian	..	..	..	..
CNS tumours				
Astrocytoma	Histology and grade; anatomical location	*H3K27M* mutation	*BRAF* status	Histological categories and grade based on ICD-O-3 classification
Medulloblastoma	..	Molecular classification	..	Molecular classification according to the ICD-O-3 classification
Ependymoma	..	..	..	..

ICD-O=International Classification of Diseases for Oncology. *ICD-O-3 classifications were originally published by Fritz and colleagues;[19] updates can be found online.

Table 2: The Lyon Paediatric Cancer Non-Stage Prognosticator Guidelines

What Are the Barriers to Adoption for These New Recommendations?

❑ May be difficult to convince PBCRs to ***devote training and resources to collecting stage*** in childhood cancers which constitute such a small percentage of their overall cancer burden

   ❑ ***Unknown feasibility*** of collecting this stage information from medical charts

   ❑ ***Unknown cost and time*** to collect childhood cancer stage data

Discussion Focus:

Background, Key Questions, & Objectives

Toronto Guidelines In Practice

Assessment of Toronto Guidelines & Next Steps

- Joanne Aitken and the Australian National Pediatric Cancer Registry **offered to put these staging guidelines to the test in the field**

☑ ***Feasibility:** are required data available?*

☑ ***Accuracy***

☑ ***Cost***

First: created "business rules"!

How do you take the recommendations from an academic article and translate those into the day-to-day job of the cancer registrar?

Childhood cancer staging for population registries

according to the

Toronto Childhood Cancer Stage Guidelines[1]

Data manager travels to main treating hospitals to collect data items needed for staging:
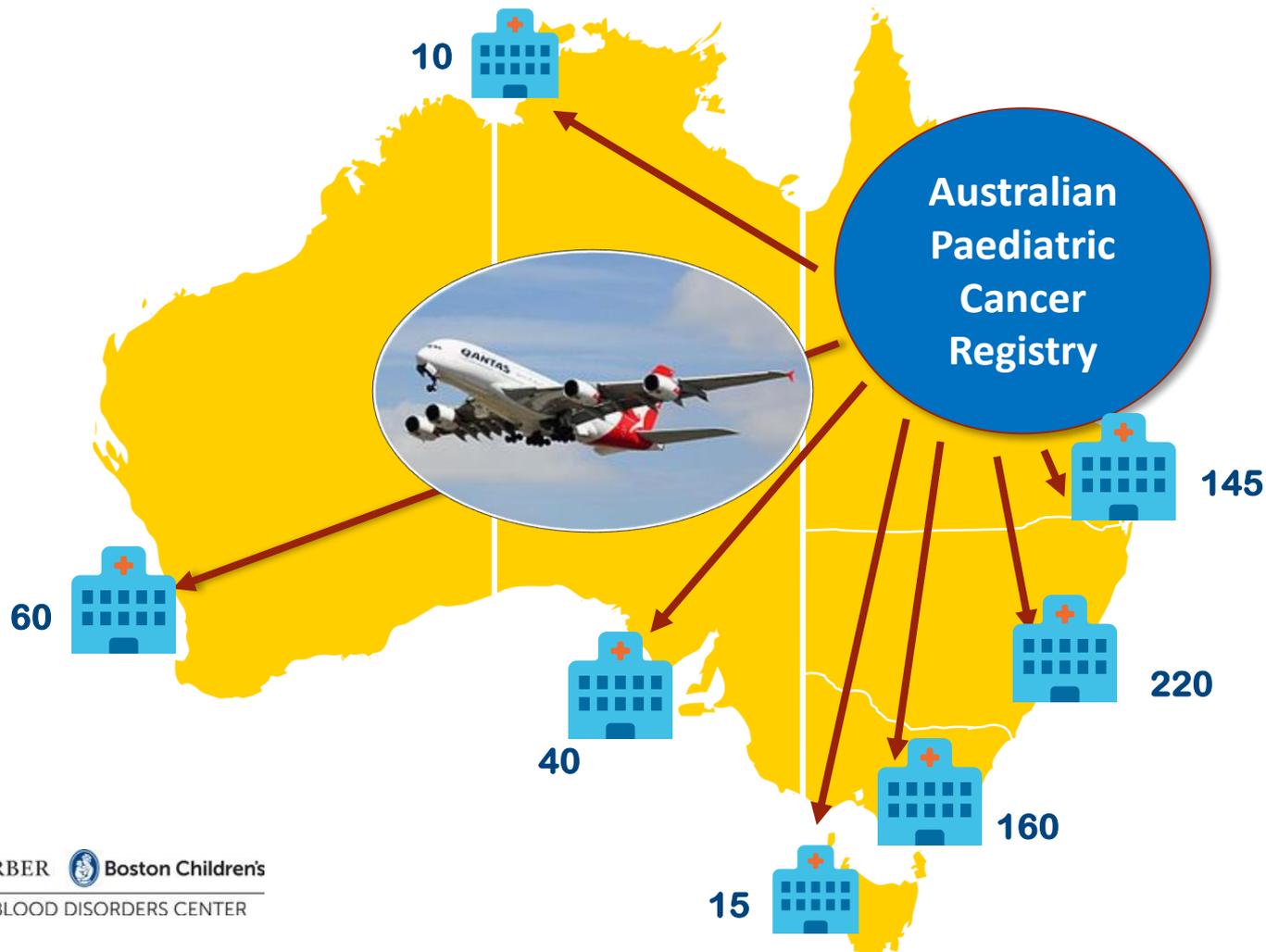
Business Rules:
Correspondence

From: Leisa O'Neill <Leisa.O'Neill@health.qld.gov.au>

Date: Sunday, December 13, 2015 at 11:29 PM

To: Sumit Gupta <sumit.gupta@sickkids.ca>

Cc: Danny Youlden <DannyYoulden@cancerqld.org.au>, Joanne Aitken <JoanneAitken@cancerqld.org.au>

Subject: APCR: Business Rules - Group 4 - NHL - medical imaging v's bone marrow reports

Dear Dr Gupta,

As you know, I have begun some data collection for the childhood cancer staging project, and I have a question regarding diagnostic imaging results versus bone marrow aspirates and trephines for children with non-Hodgkin lymphoma.

I would like to know if there is a hierarchy when it comes to comparing medical imaging to bone marrow reports? For example, if a medical imaging report states that there has been "low activity diffuse bone marrow involvement" and then I check the BMAT and it states "no bone marrow involvement", do I take the BMAT over the medical imaging?

I would be very grateful if you could help me please.

Kind regards,

Leisa

Business Rules:
Correspondence

From: Leisa O'Neill <Leisa.O'Neill@health.qld.gov.au>

Date: Wednesday, February 24, 2016 at 10:38 PM

To: Sumit Gupta <sumit.gupta@sickkids.ca>, "Frazier, Lindsay,M.D." <Lindsay_Frazier@DFCI.HARVARD.EDU>, Leisa Ward LeisaWard@cancerqld.org.au

Subject: APCR: Questions regarding: ALL, NB, Wilms and Osteo

Dear Dr Gupta and Dr Frazier,

I have been on another data collection trip and have returned with several questions.

Neuroblastoma

Can a patient have such a large tumour in the abdomen that it does not involve any vital structures (as defined by IDRF's)? The example I am referring to is: The patient has a tumour in the L upper quadrant, it compresses the L kidney but does not infiltrate it. Mass crosses midline of small bowel to R, pancreas anterior and transverse, and abuts the descending colon. Further nodules scattered throughout the abdomen. No lung or pulmonary metastatic disease or nodules. A few small foci scattered around periphery of lesion.

Wilms

A patient has had upfront nephrectomy, and then treatment was observation only. How should I stage this?

- As our BR state, COG staging is for upfront surgery then chemo; SIOP staging is for upfront chemo then surgery. This patient does not fall in either category as treatment was only observation.

My second patient had upfront chemo then a nephrectomy. At nephrectomy, there was no viable tumour. How should I stage this case?

Next case, patient had upfront chemo then nephrectomy – the histology states that there is metastatic disease in the paraaortic lymph nodes. As a coder, I would code this to metastatic. With my staging hat on, paraaortic lymph nodes are close to the kidney and are not haematogenous metastases or spread beyond the abdomen. Therefore this case can not be Stage IV – would you agree with this?

Osteosarcoma

Does "seeding within the shaft" constitute distant metastatic disease? Primary is in the R proximal tibia.

We look forward to hearing from you both. Leisa

Next: Created the Toronto Stage App

- ✓ iPad App is designed to **collect the raw data required to assign stage** directly from medical records

- ✓ **Stage is automatically assigned** based on the information collected (Tier 1 and/or Tier 2)

- ✓ This will allow **greater consistency in data collection** and particularly when assigning stage (compared to individuals trying to assign stage manually)

- ✓ Data entered into the app is **securely stored in the cloud (Microsoft Azure)**

How Did We Assign Toronto Stage?

Required data items *(e.g. diagnostic imaging, histology, blood count, bone marrow reports, cytology, CSF reports, clinical notes) were **extracted from hospital records and entered into iPad App***

Stage was assigned automatically using algorithms *based on the Business Rules*

TIER 2: ALL

CNS1	▪ No clinical signs of CNS involvement ▪ *AND* no blasts in CSF

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 ≤ 2 x WBC/RBC in blood

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 > 2 x WBC/RBC in blood

TIER 2: Neuroblastoma

[INRG Staging System]

Stage L1	- Localized tumour that does not involve any vital structures as defined by the list of IDRFs (i.e. there are no IDRFs.) - The tumour must be confined within one body compartment, neck, chest, abdomen, or pelvis...etc.
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)...etc.
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...etc.
Stage MS	Metastatic disease in patients ≤ 18 months (547 days) with metastases confined to skin, liver, and/or bone marrow... etc.

TorontoStage App:
ALL

TorontoStage App:
Cerebrospinal Fluid Results Instructions

TorontoStage App:
Hepatoblastoma

TorontoStage App:
Data Manager Comments & Status

TorontoStage App:
Export Stage

Export stage

Here you can export the entire list of cases in the system with the calculated stage values.

🔵 **Export**

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Articles

Assessing the feasibility and validity of the Toronto Childhood Cancer Stage Guidelines: a population-based registry study

Joanne F Aitken, Danny R Youlden, Andrew S Moore, Peter D Baade, Leisa J Ward, Vicky J Thursfield, Patricia C Valery, Adèle C Green, Sumit Gupta, A Lindsay Frazier

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Feasibility:
93% of Cases Could Be Staged Using Tier 2 Business Rules

Diagnostic Subgroup	Sample Size	Able To Be Staged	
		n	%
Acute lymphoid leukaemia	194	180	93%
Acute myeloid leukaemia	151	131	87%
Hodgkin lymphoma	101	95	94%
Non-Hodgkin lymphoma	132	128	97%
Ependymoma	50	48	96%
Medulloblastoma	92	89	97%
Neuroblastoma	166	159	96%
Retinoblastoma	76	75	99%
Wilms tumour	126	115	91%
Hepatoblastoma	46	46	100%
Osteosarcoma	40	37	93%
Ewing sarcoma	55	53	96%
Rhabdomyosarcoma	92	82	89%
Non-rhabdomyosarcoma	57	48	84%
Testicular	16	15	94%
Ovarian	18	17	94%

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Accuracy:
Computer Algorithm vs. Expert Reviewers

160 cases (10 of each of the 16 malignancies) selected at random

2 or 3 expert reviewers staged each case independently

✓ ***96% agreement* between computer algorithm and expert reviewers**

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Cost:
To Collect Data From Medical Records and Assign Toronto Stage

Average: *18 minutes per case*

Personnel Cost:	
Average Cost per Case:	US $ 15

Could a Registry Simply Collect Stage Recorded in the Chart by the Physician?

Not in Australia because:

➢ *Stage was **present in the record in only 39% of cases** (93% could be staged using the Toronto Guidelines)*

➢ *Which **staging system used was not recorded** in medical records (eg: whether "COG" vs. "SIOP"-stage for Wilms)*

➢ *Staging **data on the same patient were inconsistent** – different stages were recorded in different places in the record*

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Key Questions:

✓ **Can registries access the required data elements?**

✓ **Is the time required reasonable?**

✓ **Is Toronto Staging accurate and consistent?**

Next Steps

> Implementation
>> *Translated into French, Spanish, Italian, Japanese, Portuguese*
>> The Toronto Staging Guidelines have been implemented in:
>>> *Europe*
>>>> *Gemma Gatta and Kathy Pritchard-Jones are leading a study entitled "Benchista"*
>>>> *Benchmarking stage/survival in 6 cancers*
>>>>> medulloblastoma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, Wilms tumours diagnosed in a recent time period
>>> *Africa*
>>>> *Max Parkin: Côte d'Ivoire, Burkina Faso*
>>> *Brazil*
>>>> *Beatriz Camargo is implementing in 10 pediatric cancer centers*
>>> *United States – endorsed by the National Childhood Cancer Registry*

AFCRN

Règles de stadification du cancer pédiatrique pour les registres basés sur la population

basées sur
Les directives de Toronto pour la stadification du Cancer Pédiatrique [1]

Questions?

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