An application of the Toronto Childhood Cancer Stage Guidelines in three population-based cancer registries: The case of central nervous tumors

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Carlotta Sacerdote, Maria Luisa Mosso, Daniela Alessi, Franco Merletti, Giovanna Tagliabue, Anna D'Agostino, Sabrina Fabiano, Fabio Savoia, Patrizia Piga, Marcella Sessa, Francesco Vetrano, Gemma Gatta, Milena Maule.

Abstract

Background

Cancer stage is a determinant of survival of childhood central nervous system (CNS) cancers and could help the interpretation of survival variability among countries. Consensus guidelines to stage childhood malignancies in population cancer registries ("Toronto Childhood Cancer Stage Guidelines") have been recently proposed with the goal of data comparability. Indeed, stage is not systematically recorded in all registries and, when it is, different classification systems are used.

We applied the Toronto Childhood Cancer Stage Guidelines to CNS cancer cases of three population based cancer registries with the aim of evaluating the feasibility of staging this type of cancer and the critical points in the classification of CNS tumors.

Procedures

The Toronto Childhood Cancer Stage Guidelines were applied to 175 CNS patients, diagnosed from January 1, 2002 to December 31, 2014 in three cancer registries in Italy, and the percentage of cases that could be staged was assessed.

Results

One hundred eight of 126 (86%) medulloblastomas and other embryonal CNS cancers and 22 of 49 (45%) ependymomas were staged. Using these guidelines, survival of children with localized tumors could be discriminated from that of children with metastatic disease.

Conclusions

The use of the Toronto Childhood Cancer Stage Guidelines is feasible for staging medulloblastoma in Italian population based cancer registries, whereas it is more difficult for ependymomas. In Italy, cerebrospinal fluid examination, one of the decisive tests to stage CNS tumors, is not routinely performed as a first line diagnosis procedure in ependymoma pediatric patients.

A similar exercise by a larger number of cancer registries in different countries could suggest improvements in the childhood cancer staging system.

Abbreviations

CCRC Childhood Cancer Registry of Campania
CCRP Childhood Cancer Registry of Piedmont
CNS central nervous system
CSF cerebrospinal fluid
MRI magnetic resonance imaging
SEER Surveillance, Epidemiology, and End Results
VCR Varese Cancer Registry
WHO World Health Organization

1 INTRODUCTION

In Europe, childhood cancer survival figures assessed by population based cancer registries show major geographical differences in some cancer groups such as central nervous system (CNS) tumors.1

Cancer stage, that is, the anatomical extent of the disease at diagnosis, is one of the most important determinants of survival, fundamental to interpret survival variability among countries. Unfortunately, stage is not systematically recorded in all registries and, when it is, the classification system is not always the same, especially for children and adolescents. Children and adolescent cancer registries record stage according to the adult TNM staging classification or using disease specific staging systems that differ among countries and/or specialized scientific societies.2 The TNM classification, developed and maintained by the Union for International Cancer Control (UICC), is a globally recognized standard for many adult cancers, but it is not applicable to the majority of pediatric cancers.3, 4 Different disease specific staging systems have been developed for several childhood cancer types with local or national validity, with the aim of guiding clinicians in the choice of treatment for individual patients, but an international standard system for cancer registries is still lacking. Furthermore, the clinical staging systems in use often require the examination of specific molecular features that may be difficult to find in the sources of information of cancer registries.5

Since accurate information on stage is essential to compare survival in different time periods and countries, and given this is of particular interest for children and adolescent cancer, a panel of international pediatric cancer and cancer registry experts met in Toronto in 2014 to propose guidelines to record childhood cancer stage in a standardized way.2 Such guidelines are explicitly intended to be applied by population cancer registries with the goal of data comparability and interpretation of inter registry and international differences. The Toronto experts identified a staging system for 18 childhood cancer types. The most important novelty of the proposed guidelines is a tiered organization, with a more detailed system for well resourced cancer registries and a less detailed system for registries with limited resources. Inter registry comparability is ensured by the possibility of collapsing higher tier categories into lower ones.2

The Toronto Childhood Cancer Stage Guidelines (Toronto guidelines hereafter) are of particular interest for CNS cancers because of the heterogeneous survival of this type of neoplasms across countries.1 Recently proposed staging systems for CNS tumors are mostly based on molecular features6-9 and thus not particularly suitable for cancer registries. Furthermore, the World Health Organization (WHO) classification of CNS tumors, published in 2016 and widely adopted in international settings, is a morphological classification, where molecular parameters are used in addition to traditional histology to classify many tumor types including gliomas, ependymomas, and medulloblastomas.9

The American Surveillance, Epidemiology, and End Results (SEER) proposed a simple staging system for all tumors, which included CNS tumors, classifying localized, regional or metastatic tumors, suitable for general cancer registries.10

In this study, we have applied the Toronto guidelines to all recent cases of CNS tumors of a general population based cancer registry and two specialized childhood cancer registries in Italy with the aim of (a) evaluating the feasibility of staging cancer using the existing clinical records collected for the routine registration activities, (b) comparing the performance of the Toronto guidelines with the SEER staging system in predicting mortality from medulloblastoma, and (c) assessing critical points and providing suggestions to improve classification of CNS tumors.

2 METHODS

Cancer registration in Italy is based on the data of 48 population based Italian cancer registries, with very different coverage areas (from municipal areas to entire regions). Approximately 70% of the national territory is currently covered by cancer registries, with different periods of registration, ranging from very old (Childhood Cancer Registry of Piedmont [CCRP], starting in 1965) to very recent ones (Benevento Registry, starting in 2017). There are two active regional specialized childhood cancer registers, CCRP and the Childhood Cancer Registry of Campania (CCRC). These were included in the study as well as the Varese Cancer Registry (VCR) one of the oldest registries operating in Italy (active since 1976). These three registries were selected to test the feasibility of cancer staging in different Italian geographical areas and cancer registry settings.

We included CNS cancer cases, aged 0 19 years, diagnosed from January 1, 2002 to December 31, 2011 in CCRP11 and VCR,12 and those diagnosed from January 1, 2008 to December 31, 2014 in CCRC.13

In the context of CNS tumors, the Toronto guidelines proposed a staging system for medulloblastoma (and other CNS embryonal tumors) and ependymoma. For astrocytomas, no staging system was proposed, because for these tumors the main prognostic factors are typically available to cancer registries, and include histological type, WHO grade, and site of disease.5

The Toronto guidelines proposed two levels of staging (tiers): lower tiers are more basic and require limited clinical information, whereas higher tiers are more detailed and require a comprehensive consultation of the clinical documentation.

For medulloblastoma and other CNS embryonal tumors, as well as for ependymoma, the following tiers were proposed2:

- Tier 1: M0 or localized/M+ or metastatic,
- Tier 2: M0/M1/M2/M3/M4.

The difference between medulloblastoma and ependymoma lies in the prognostic factors not directly related to staging, such as extent of residual disease after resection for the former and the type of resection, if performed, for the latter. Although not involved in the above tiers, data on residual disease are recommended information to collect as a predictor of prognosis.

In the absence of visible disease beyond the diagnostic magnetic resonance imaging (MRI) of brain and spine and in the absence of malignant cells in cerebrospinal fluid (CSF), M0 is applied in Tier 1 and Tier 2. In Tier 1, all metastatic diseases, including malignant cells in CSF, are classified as M+. In Tier 2, in the presence of malignant cells in the CSF, M1 is applied, whereas M2 is applied if

there are visible metastases in the brain, M3 if they are in the spine, and M4 if they are outside of the CNS.

The SEER staging system classifies the tumors of brain and cerebral meninges as follows: 1: localized only, 2: regional, 7: distant site(s)/lymph node(s) involved, and 9: extension or metastasis unknown. To classify a cancer in stage 1 or 2, it is necessary to know the precise localization of the tumor and if the tumor crossed the midline.

We selected all cancers recorded in the three registries with ICDO3 morphology 9470/3, 9471/3, 9474/3, 9362/3, 9473/3, 9508/3, 9383/1, 9391/3, 9392/3, 9393/3, and 9394/1 (Table 1), and we re evaluated all the available clinical documentation useful to determine both the Toronto guidelines and the SEER stages.

In Italy, registration is based on active case finding. The minimum clinical information set required for the routine registration of cases in Italian cancer registries includes pathology reports, death certificates, and hospital discharge data chart. Other clinical information is often collected by cancer registries, particularly for some cancer sites, including hospital records, cytology results, imaging results, surgical reports and therapies. Specialized pediatric cancer registries in Italy usually collect more clinical information than general population cancer registries. In addition to pathology reports and death certificates, all clinical records of diagnostic hospital admissions are obtained. However, typically registries do not have access to the full medical records for all registered cases, and not all the clinical data examined for registration are electronically recorded into the registry database. In this study, the definition of the stage was obtained perusing all existing clinical records originally collected for the routine registration activities in order to retrieve information not readily available from the registry records.

We estimated the cumulative survival of patients with medulloblastoma and other CNS embryonal tumors for different tiers using both the Toronto guidelines and the SEER classification (localized and metastatic). The median survival for stage classification was estimated using the Kaplan Meier method. In the survival analysis, Tier 2 was grouped in three levels to maintain an adequate sample size in all strata. For the same reason, the SEER classification was grouped into two levels, localized and metastatic. The difference in overall survival among stages was assessed using the log rank test. All analyses were performed using SAS 9.2 and STATA 11.

3 RESULTS

Ninety six medulloblastomas, 30 other embryonal CNS cancers, and 49 ependymomas were identified. One hundred eight of 126 (86%) medulloblastomas and other embryonal CNS cancers and 22 of 49 (45%) ependymomas were staged (Table 2).

TABLE 2. Successful classification of medulloblastomas, other embryonal cancers, and ependymomas in two specialized cancer registries (CCRP and CCRC) and one general population cancer registry (VCR)

In both CCRP and CCRC, when the cancer was staged at Tier 1, it was always possible to classify it also at Tier 2 (118/118); In the VCR, it was possible to stage both tiers for all cases but one (11/12), staged only at Tier 1. The residual disease was assessed in almost all the staged patients in CCRP and VCR (129/130), but only in six cases (6/62) in CCRC.

With the exception of VCR, the percentage of successful classification of medulloblastomas and other embryonal CNS cancers was systematically higher than the classification of ependymomas.

The low rate of staged ependymomas both in CCRP and CCRC (54% and 24%, respectively) is mainly due to the lack of information on the CSF analysis in clinical notes (in the majority of cases, the examination probably had not been performed). Also among medulloblastomas, a percentage of cases could not be staged at all because of missing information on the CSF analysis, the problem for medulloblastomas is however less severe than for ependymomas.

Table 3 shows how the SEER and the Toronto guidelines system performed in staging medulloblastoma patients. Both systems failed to classify the same 14 cases, because both would have required the CSF analysis that in these cases was either not performed or, if performed, not available in the clinical documentation collected by the cancer registry. Except for one case (classified as metastatic by the SEER system and M0 by the Toronto guidelines), the other 32 cases were classified as metastatic by both systems. The Toronto guidelines Tier 2, however, allowed further distinctions between M1 and M4.

The Kaplan Meier survival curves by stage are shown in Figure 1A D. Figure 1A shows that Toronto guidelines Tier 1 is capable of discriminating children with localized tumors and higher survival from children with metastatic disease. SEER staging yielded the same survival pattern (only for one patient, stage was discordant in the two systems; data not shown). Toronto guidelines Tier 2 yields less clear results (Figure 1B), with no substantial difference in survival between children with medulloblastoma stages M0/M1 and M2/M3. However, the sample size is small and may be partly responsible for the overlap of curves. Figure 1C shows that the residual disease after surgery, also if it is not part of the staging system, is a strong predictor of survival of children affected by medulloblastoma, at least after 24 months of follow up. Notably, patients with tumors that were not staged seemed to have lower survival, more similar to that of patients with metastatic than localized tumors.

4 DISCUSSION

Cancer stage is an important prognostic factor for childhood cancer and crucial to interpret survival variability among countries. The Toronto guidelines are a practical tool for population cancer registries to collect standardized information on stage at diagnosis for childhood cancers, and to overcome some of the obstacles hampering staging in cancer registries.2

Our results indicate that the application of Toronto guidelines is feasible to stage medulloblastoma in three different Italian population based cancer registries using the clinical records available for the routine registration activities. In our experience, we found the use of the Toronto guidelines more difficult in staging ependymomas. The proposed classification is indeed derived from a staging system originally proposed for medulloblastomas in 1969 by Chang and updated in 1977 by Harisiadis.14, 15

We are aware of one other attempt to apply the Toronto guidelines and to measure the feasibility and validity of this staging system in the Australian population based cancer registry.16 In this childhood cancer registry, the application of the Toronto guidelines resulted in 97% and 96% staged patients for medulloblastomas and ependymomas, respectively. The percentage of staged patients at Tier 2 in our population was lower than that in the Australian registry.

The decisive examinations to attribute CNS tumor stage for all the tiers are MRI and CSF analysis. MRI is routinely performed in all CNS cancer pediatric patients, and the MRI report is usually present in the clinical notes. However, in ependymoma patients, CSF analysis as a first line diagnostic procedure is subject of controversy. Some authors recommend performing only MRI

because virtually all children with disseminated disease at diagnosis have a bulky metastatic disease.15 A study by Fangusaro and colleagues highlighted the extreme rarity of ependymoma patients with microscopic metastases diagnosed with CSF cytology only.16 In our study, 10% of patients that presented metastasis at diagnosis were identified as having a bulky disease on postcontrast spinal MRIs. No patient without metastases tested positive to CSF cytology.17 In contrast, other authors strongly support the use of CSF analysis as a first line diagnosis procedure,18 showing a relevant number of patients with metastatic ependymoma identified only with CSF cytology. This lack of agreement on the diagnostic procedure is probably reflected in geographical and temporal differences on the use of CSF analysis in children with ependymoma. In the Piedmont and Campania regions, CSF analysis is rarely (if ever) performed as a diagnostic first line examination in ependymoma patients. In Lombardy, on the contrary, all children with ependymoma underwent CSF analysis, possibly reflecting different medical staff opinions on the procedure.19

However, there is a clear indication to perform the CSF analysis in all children with medulloblastoma. Moreover, a CSF analysis is recommended about 2 weeks after surgery to avoid false positive cytology.20 The lower proportion of staged cases of medulloblastoma in Italian registries compared to the Australian study may be due to missing information on CSF analysis. This is a consequence of the procedures adopted by registries, aimed at case definition and not at following up cases after the diagnosis has been assessed. Therefore, CSF and other tests performed after treatment are likely to be absent in the clinical documentation gathered by the registries.

The Toronto guidelines staging encounters the same problems of the SEER staging when the information about CSF analysis is not available for patients without distant metastasis, although, for the staged cases, the Toronto guidelines gave more detailed results using the same clinical information. Furthermore, in the SEER classification, defining if a stage is localized or regional is sometimes difficult because of the difficult interpretation of laterality, for instance for the brain stem. Indeed, only in the SEER grading stage manual for CNS it is required to evaluate the possibility that the tumor has crossed the midline.

Our study shows that the Toronto guidelines system for CNS cancer staging in cancer registries may be difficult to apply, especially for some cancer types, because it is based on diagnostic examinations that are not universally and uniformly accepted in the clinical practice. Data on clinical tests performed after diagnosis confirmation and after surgery, additional to information acquired to perfect the definition and registration of a case, may be difficult to retrieve for cancer registries.

Our results suggest that Toronto guidelines Tier 1 could be easily applied to stage ependymoma and medulloblastoma patients using the results of diagnostic MRI of brain and spine that are typically available in the clinical records also in the absence of CSF analysis, as it is often the case for ependymomas.

In conclusion, since accurate staging is essential to compare survival in different time periods and countries, the initiative of the Toronto guidelines specific for cancer registries is extremely important. This pilot study on the application of Toronto guidelines in general and specialized cancer registries highlights the feasibility of this approach and some critical points. For instance, we found that results of the CSF analysis are difficult to obtain at least in two out of the three Italian registries participating in the study and we hypothesize possible reasons related to the application of different protocols by clinicians or/and the poor documentations made available by the registry. For the success in the application of the Toronto guidelines, collaboration with the clinicians and the national association of pediatric oncologists is crucial.

We believe that a similar exercise by a larger number of cancer registries in different countries could suggest improvements and changes to the childhood CNS cancer staging system through a virtuous iterative process.21

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1Gatta G, Peris Bonet R, Visser O, et al. Geographical variability in survival of European children with central nervous system tumours. *Eur J Cancer*. 2017; 82: 137 148.

2 Gupta S, Aitken JF, Bartels U, et al. Paediatric cancer stage in population based cancer registries: the Toronto consensus principles and guidelines. *Lancet Oncol*. 2016; 17(4): e163 e172.

3Brierley J, Gospodarowicz M, Wittekind C. The TNM Classification of Malignant Tumours. 8th ed Oxford, UK: Hoboken, NJ: John Wiley and Sons Inc; 2017.

4Greene FL, Sobin LH. A worldwide approach to the TNM staging system: collaborative efforts of the AJCC and UICC. *J Surg Oncol*. 2009; 99(5): 269 272.

5Thompson EM, Hielscher T, Bouffet E, et al. Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. *Lancet Oncol*. 2016; 17(4): 484 495.

6Capper D, Jones DTW, Sill M, et al. DNA methylation based classification of central nervous system tumours. *Nature*. 2018; 555(7697): 469 474.

7Cairns J. Pediatric medulloblastomas: classification, therapeutics, and management. *UBCMJ*. 2018; 9.2(8 11).

8Korshunov A, Witt H, Hielscher T, et al. Molecular staging of intracranial ependymoma in children and adults. *J Clin Oncol*. 2010; 28(19): 3182 3190.

9Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. *WHO Classification of Tumours of the Central Nervous System*. Revised 4th ed. WHO Press, 1211 Geneva 27, Switzerland WHO Classification of Tumours. Vol. 1. 2016.

10https://seer.cancer.gov/tools/ssm/SSM2018-BRAIN.pdf. Accessed February 12, 2020.

11Isaevska E, Manasievska M, Alessi D, et al. Cancer incidence rates and trends among children and adolescents in Piedmont, 1967–2011. *PLoS One*. 2017; 12(7):e0181805.

12Steliarova Foucher E, Colombet M, et al. International incidence of childhood cancer, 2001 10: a population based registry study. *Lancet Oncol*. 2017; 18(6): 719 731.

13www.santobonopausilipon.it/content/registro-tumori-infantili-regione-campania-rtic

14Chang CH, Housepian EM. An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. *Radiology*. 1969; 93(6): 1351.

15Harisiadis L, Chang CH. Medulloblastoma in children: a correlation between staging and results of treatment. *Int J Radiat Oncol Biol Phys*. 1977; 2(9 10): 833 841.

16Aitken JF, Youlden DR, Moore AS, et al. Assessing the feasibility and validity of the Toronto Childhood Cancer Stage Guidelines: a population based registry study. *Lancet Child Adolesc Health*. 2018; 2(3): 173 179.

17Zacharoulis S, Moreno L. Ependymoma: an update. *J Child Neurol*. 2009; 24(11): 1431 1438.

18Fangusaro J, Van Den Berghe C, Tomita T, et al. Evaluating the incidence and utility of microscopic metastatic dissemination as diagnosed by lumbar cerebro spinal fluid (CSF) samples in children with newly diagnosed intracranial ependymoma. *J Neuroncol*. 2011; 103(3): 693 698.

19Moreno L, Pollack IF, Duffner PK, et al. Utility of cerebrospinal fluid cytology in newly diagnosed childhood ependymoma. *J Pediatr Hematol Oncol*. 2010; 32(6): 515 518.

20Massimino M, Biassoni V, Gandola L, et al. Childhood medulloblastoma. *Crit Rev Oncol Hematol*. 2016; 105: 35 51.

21Gatta G, Botta L, Trama A, Pritchard Jones K, The Pilot Study Group. The stage for childhood cancers: the JARC pilot study. Oral communication at the ENCR Scientific Meeting and General Assembly, 26 28 September 2018, Copenhagen, Denmark.