1   Title: **Staging childhood cancers in Europe: application of the Toronto stage principles for**

2   **neuroblastoma and Wilms tumour. The JARC pilot study.**

3   Short title: **Toronto stage principles for childhood cancers**

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22   **List of abbreviation:**

CC	Childhood cancer
COG	Children's Oncology Group
CRs	Population-based cancer registries
ENCR	European Network of Cancer Registries
EoD	Extent of disease
IDREFs	Image defined risk factors
INRG	International Neuroblastoma Risk Group
INT	Fondazione IRCCS 'Istituto Nazionale dei Tumori'
JARC	European Joint Action on Rare Cancers
NB	Neuroblastoma
NWTSG	National Wilms' Tumor Study Group
SIOP	International Society of Paediatric Oncology
SIOPEN	European society of paediatric oncology neuroblastoma
TG	Toronto consensus principles and guidelines
WT	Wilms tumours

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31   **Abstract**

Background

The "Toronto consensus principles and guidelines" (TG) provided paediatric-specific staging system affordable by population-based cancer registries (CRs). Within the European Rare Cancers Joint Action, a pilot study of the application of TG for childhood cancer (CC) was conducted to: test the ability of CRs to reconstruct stage, describe stage across countries and assess survival by stage.

Procedure

Twenty-five CRs representing 15 countries contributed data on a representative sample of patients with neuroblastoma (NB) and Wilms tumours (WT) <15 years, diagnosed between 2000 to 2016. Outcome was calculated by Kaplan Meier method and by Cox regression model.

Results

Stage was reconstructed for 95% of cases. Around half of the children had localised or loco-regional disease at diagnosis. The proportion of metastatic cases was 38% for NB and 13% for WT. Three-year survival was >90% for loco-regional cases both of NB and WT, 58% for NB M-stage and 77% for WT stage-IV. Older age was associated with more advanced stage.

Conclusions

European CRs were able to reconstruct stage according to the TG. Stage should be included in the routine collection of variables. Stage information had clear prognostic value and should be used to investigate survival variations between countries or over time.

Background

The most recent EUROCARE study showed that 5-year survival for all CC combined is increasing in Europe[1]. Despite these improvements, survival disparities persist between European countries and regions: from 70% in Eastern Europe

to 81% in Northern Europe. One of the reasons that may explain survival differences between countries and over time could be differences in tumour stage at presentation [2], an information difficult to collect, as most population-based cancer registries (CRs) use TNM staging systems, which are not applicable to the majority of CC [2]. A standardised way to assign tumour stage, that takes account of the special characteristics of cancer in childhood and can be used for complete collection of this variable by CRs, is crucial for comparison and interpretation of survival differences.

Recently, the "Toronto consensus principles and guidelines" (TG) provided recommendations on which paediatric-specific staging systems should be adopted by CRs for each of the major childhood malignancies [3].

Within the European Joint Action on Rare Cancers (JARC) [4], we conducted a pilot study to test the use of the TG by CRs and to undertake analysis of survival by tumour stage in the two commonest extra-cranial childhood solid tumours, namely neuroblastoma (NB) and Wilms tumour (WT). The aims of this study were:

- To involve European CRs in applying the TG to a defined set of incident cases;
- To describe the distribution of stage at diagnosis by country and overall survival by stage;
- To describe the data sources used, the resources required and any barriers to obtaining the clinical data needed to assign the TG;
- To enable a future international benchmarking study of survival by stage to be conducted.

The experience and learning gained during the pilot study are expected to support wider adoption of the TG for future international comparative incidence and outcome studies between CRs.

Methods

We asked registries to provide information on stage for at least 10 consecutive cases each of NB and WT. For the larger registries, with more than 10 cases/year of each tumour type, we required all cases incident in the most recent and complete year of incidence. Smaller registries had to include all the cases diagnosed in a sufficient number of years, to achieve the required minimum cases. Depending on the size of the population covered and the tumours rarity, some registries included cases back to the early 2000s. Registries contributing data were described in Table 1. All cases

81 incident in the relevant time period for each registry was included with the exception of cases defined of the basis of

82 death certificate only.

83 A protocol with the variables to be collected was agreed upon with the CRs. Variables required were age, sex, codes of

84 topography and morphology [5], imaging and examinations considered for defining the stage at diagnosis, TG stage

85 (Supplementary material:Table S1) [3], follow-up for vital status and date of death/last contact. The registries were also

86 asked to report sources used for assigning stage e.g. clinical records, pathology reports, administrative files. CRs had to

87 be assigned tumour stage at diagnosis for NB and after surgery for WT. For the latter it was required to assign the prefix

88 'y' in case of neoadjuvant chemotherapy. Exception was WT in stage M. The staging manual for registry staff, was

89 made available by the Australian CR [6] and was used by all the participants along with the agreed study protocol. The

90 TG include a nested two-tiered level system to define stage [3,6]: Tier 2 staging systems are more detailed and intended

91 for use in high resource settings. Tier 1 system is based on collapsing Tier 2 system categories to preserve

92 comparability across registries, The full details of Tier 1 and Tier 2 staging criteria for each cancer type are available

93 elsewhere [3,6]. This study invited use of Tier 2, however if this were not possible, Tier 1 could be adopted. Those

94 responsible for the data collection were physicians or paediatricians or registrars together with clinicians. A central 'help

95 desk' for discussing possible problems and answering specific questions was provided at the Fondazione IRCCS

96 'Istituto Nazionale dei Tumori' (INT), however, the helpline was never utilised, because CRs were assisted by physicians

97 or paediatric oncologists. Revision of the staging data, asked to registries with a low proportion of NB with stage M and

98 a low proportion of WT in localised stage, confirmed the staging. Cases were provided by CRs as individual record form.

99 For all cases, we requested the most recent follow-up information for survival. However, they had to assure at least

100 three years of follow-up.

101 Descriptive analyses of proportions of NB and WT cases by stage for each country and overall by age were performed.

102 Due to the small number of cases, countries were anonymized in Figure 1 to avoid improper formal comparisons.

103 Overall survival was estimated using Kaplan Meier method. Log rank test was used to identify significant differences in

104 survival between stages. In the survival analyses, cases from Hungary and Portugal CRs (both cancers) and Germany

105 (NB only) were excluded because they could not assure three years of follow-up. Multivariable Cox regression were

106 carried out to estimate relative risk of death by age, sex, and stage, also including country as an adjustment variable.

107 95% confidence intervals were shown for single variable levels, while likelihood ratio test was used to evaluate the

108 global significance of the included variables.

109

110 **Results**

111 Twenty-five CRs from fifteen countries contributed data. Overall, 621 NB and 494 WT were included in the analysis.

112 Table 1 shows the distribution of cases by country together with the period of incidence (year of diagnosis) and the

113 corresponding follow-up. Five countries, two regionally covered (Italy and Spain) and three paediatric (specialized) and

114 national (France, Germany and Greece) contributed > 100 cases, each. The other registries provided a number of cases

115 ranging between 20 (Denmark) and 34 (Belgium). For 3% of NB and 8% of WT cases CRs could not assign the stage,

116 because no access to the medical record of the main hospitalization . Registries were able to define stage according to

117 the most detailed Tier 2. Exceptions were the German CR which used Tier 1 stage for NB, and 5 NB and 8 WT cases

118 scattered in other 5 registries.

119 *Source of data*

120 Data sources used to assign stage were clinical records, administrative files, pathological reports and clinical study data

121 bases. Table 2 shows how much the specific sources of data were used by tumour type. Except for Germany that used

122 the Clinical trial/study report for staging the tumours, both clinical records and pathological reports were used to define

123 stage in almost all the other NB patients and about 50% of the WT patients. Moreover for WT 17% of the cases were

124 staged using only pathological report.

125 The assignment of stage was undertaken by paediatricians, medical doctors or registrars in cooperation with clinicians.

126 Revision of the staging data was asked only from those registries with a low proportion of NB with stage M and WT in

127 localised stage. The revision confirmed the staging.

128 *Neuroblastoma.*

129 CRs were able to assign stage in 604/621 (97%) of cases. About half 300/621 (49%) of children were diagnosed with

130 localised (L1) or regional disease (L2/locoregional) (Table 3). However, the proportion of metastatic tumour, stage M,

131 was relatively high (38%), with a further 11% diagnosed with metastatic disease in the first 18 months of life (infants) [6],

categorised as stage MS. Figure 1A shows the geographical variability of the distribution of stage. Stage M accounted for the highest proportion of cases (ranging from 36% to 64%) in all countries, except for four countries.

Infants were more likely to be diagnosed at L1 (36%) or L2 (24%) stages. The disease was more aggressive in older children: more than half of them diagnosed at stage M (Table 4).

Three-year survival, based on all 459 cases, was the highest for stage L1-2 (99% and 92%, respectively), followed by stage MS (84%) and M (58%). In all stages, infants had the highest 3-year survival (from 100% in L1 to 70% in M). Children aged >18 months with stage M had the lowest survival rate (53% and 56%).

There were significant differences in survival between stages L1 vs L2 and MS vs M, but not between L2 and MS (log rank p=0.28) (Table 4).

The Cox analysis (Table 5) showed a significant and strong increase of the adjusted risk of dying for stage L2, MS and M, with respect to stage L1. Children aged >18 months had a two-fold increased risk of dying compared to those aged 0-18 months.

Wilms tumours

In this study as in Europe, children with WT are mainly treated (78%) according to the International Society of Paediatric Oncology (SIOP) Renal Tumour Study Group protocols that use preoperative chemotherapy for a number of weeks prior to nephrectomy, with local (abdominal) tumour stage assigned on the surgical specimen [7]. In this situation, the local stage is pre-fixed with 'y'. Some centres routinely use the alternative treatment approach that is standard in North America, of upfront nephrectomy with staging of a "chemo-naïve" tumour specimen [7]. Only 18% of patients in this study   received immediate nephrectomy, 4% had no information on the treatment approach followed, for most of them stage was also missing.

The majority (79%) of children were diagnosed with localised tumours: 40% with stage I/yI, 21% with stage II/yII and 19% with stage III/yIII (Table 3). Sixty-one percent of infants, here defined as aged <1 year, were diagnosed with Stage I/yI and remarkably there were only 2 cases with metastases at presentation. Children aged 5-14 had the highest proportion of metastatic disease (stage IV) (24%). In nearly all countries, stage I/yI was the most common stage, ranging between 60% and 24% (Figure 1b). Three-year overall survival was favourable, at 93% for the overall population and varying by stage between 97% (stage I/yI) to 77% (stage IV).

159   There were significant differences in survival between stages, except I/yI vs II/yII (Table 4).

160   The adjusted risk of dying (Table 5) increased by the extent of disease: III/yIII and IV by 7 and 18 times versus stage I/yI

161   (p<0.0001).

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163   **Discussion**

164   This is the first population-based study describing the feasibility of assigning stage according to the TG for two

165   paediatric solid cancers in several European countries. Information on tumour stage in children with WT and NB was

166   assigned in accordance with the guidelines in almost all the cases and collected from European registries. In only 5% of

167   cases, it was not possible to assign tumour stage with the information accessible to the CR. Almost half of NB and 79%

168   of WT cases presented with localised stage at diagnosis and nearly half children with NB and slightly more than 10%

169   with WT were diagnosed with distant metastases. Three-year survival in the study sample was 93% for WT and 80% for

170   NB. Toronto stage was highly predictive of survival: 3-year survival varied significantly between 99% (L1), 92% (L2) and

171   58% (M) for NB and from locoregional (I/yI+II/yII+III/yIII) 96% and 77% (IV) for WT.

172   In the literature, there are few population-based studies illustrating survival by stage for CC, and, to our knowledge,

173   none addressing geographical differences in the distribution. Studies conducted by paediatric or non-specialized CRs

174   using different types of stage (extent of disease, TNM, Evans stage, INSS) reported a proportion of missing from 0 to

175   36% [8-15]. Compared to the Australian experience [16] which applied the TG for the registration of stage in the national

176   paediatric registry, we found for NB a similar proportion of L1 (27% vs 26%) and a lower proportion of stage M (38% vs

177   51%) (see Table 3). For WT, we showed an earlier stage distribution (more Stage I and less Stage III) in the European

178   than the Australian study (stage I/yI 40% vs 29% and stage III/yIII 19% vs 31%). In the Australian study, 51% of children

179   received preoperative chemotherapy (vs 78% of our study) [16]. Five-year survival for the Australian children with NB

180   was 98% in L1, 87% in L2, 60% in M stages [16], and 76% overall close to the 3-year survival in our study (80%, see

181   Table 3). For WT, 5-year survival was very good for stages I/yI to II/yII and for all stages combined, all over 91% [16],

182   similar to 3-year survival in our study (93%, see Table 4). Survival for stage IV was higher in Australia (83%) [16] than in

183   our study (77%) .

184   We found a fair heterogeneity in the distribution of stage across countries for both NB and WT which may partly be

185   explained by differences in the distribution of age at the time of diagnosis. Infants with NB and WT arrived at earlier

stage at diagnosis, see Table 2. The proportions of infants with NB in the four countries with lower proportion of M, was slightly over the overall proportion of infants in the study (52%). For WT there was no difference in the proportion of cases diagnosed as infants across countries. However, the small sample size of this pilot study allows to put in evidence some heterogeneity in stage attribution, but not to interpret differences between single countries.

In most registries, stage was recorded thanks to informative sources and competent staff. Nevertheless, in some cases it was required to review stage: 4 CRs with relatively low proportion of stage M and 1 CR with none case diagnosed in L2 Stage in NB. Cases were all queried and re-confirmed with the CRs - one CR explained that the absence of L2 suggested the possibility that some L1 cases might have been L2, because the invasion of vital structures was not easy to detect from the clinical records which lacked of some definitive imaging.

Our population-based survival values are lower than those reported in the literature by clinical trial/studies [17-24]. This is expected, since clinical studies are always carried out in a controlled setting and in specialized centres and aim to provide the highest outcome achievable and evaluate the efficacy of a treatment protocol. Furthermore, one cannot exclude the selective inclusion of cases, based on a set of clinical criteria.

Population-based studies provide instead the overall survival in a defined population and therefore evaluate the efficacy of the regional health programmes.

In a review [17], based on 3,600 children with WT registered in the SIOP 2001 trial, 5-year survival across stages I-III ranged between 98% and 90% and it was 82% for stage IV (Table S2). However, infants, patients with bilateral tumours and patients that could not adhere to the protocol were excluded from the analysis. The most important prognostic factors for recurrence leading to reduced survival were the histology risk group (blastemal type remaining after chemotherapy or diffuse anaplasia) and advanced tumour stage (III & IV). In the SIOP WT database 14% of cases, of all stages, were in this high risk histology group. Five-year survival for those in stage IV was 35%, while for those in low or intermediate risk were 94% and 89%. The SIOP WT database shows almost the same distribution by stage as our study (Table S2).

From the European society of paediatric oncology neuroblastoma (SIOPEN) , 661 NB cases analysed by the International Neuroblastoma Risk Group (INRG) , 5-year overall survival was 96% for patients diagnosed at INRGSS stage L1 and 89% for stage L2, outcome and the distribution by L1 and L2 were similar to our study in which the

locoregional cases were defined according to the 'surgical risk factors' [18]. In the study by Kholer at al., 5-year survival in unresectable localised NB with non-amplified MYCN was 87.5%, even better for younger children and favourable histology [19]. In Infants [20,21] with amplified MYCN from stage 2-4, 2-year survival was 30%, while in infants with non-amplifed MYCN and with stage M and MS was >90%. Children with localised resectable tumours, age <18 months was more common and other prognostic variables as the urine tests (HVA, VMA), DNA index, serum LDH were not altered or favourable in a high percentages of the children in the study. From clinical studies we know that patients are stratified by risk factors, at least by age, stage, resectability, MYCN and histopatological features and that age and stage are related to the other prognostic factors. Actually, they are determinant for the choice of the treatment protocol [22-24].

One merit of our study is that we increased the awareness and dissemination of the TG in stage recording for paediatric cancers in several European CRs. To encourage the routine collection of stage according to TG by the CRs, it is necessary to get the endorsement of their respective International and National associations. Both the International Association of Cancer Registries (IACR) [http://www.iacr.com.fr/index.php?option=com_content&view=article&id=153&Itemid=657] and the European Network of Cancer Registries (ENCR) [https://encr.eu/news/encr-endorsement-toronto-childhood-cancer-stage-guidelines] are promoting the collection of stage for all cancer cases, including paediatric cancers with the TG. The ENCR will ask stage for childhood cancers according to the TG in their next call for data [https://encr.eu/call-for-data]. Furthermore, the ENCR training courses now include the Toronto Staging Guidelines in the programme [https://encr.eu/news/encr-jrc-training-material-coding-cancer-available-now-encr-website].To collect stage at diagnosis for cancer cases is now more feasible thanks to the increase of sources linkage for CRs. A new project 'International Benchmarking of Childhood Cancer Survival by Stage' is starting to promote the collection of childhood cancer stage in Europe [https://www.childrenwithcancer.org.uk/childhood-cancer-info/we-fund-research/projects-we-fund/understanding-why-childhood-cancer-survival-varies-between-countries/] for the major solid paediatric tumours in order to promote its routinery collection. The study will then verify the applicability of TC in other continents like Japan, Canada, Brazil and US CRs which accepted to participate together with an higher number of the European CRs. Also, the project will promote the linkage with key national clinical/hospital database in collaboration with SIOPE and National specific societies.

239 SIOPE has endorsed and is encouraging the active joint work of CRs and clinical registries to improve data quality and

240 completeness with more clinical information on first line therapy and relapse [25].

241 The major achievement of our work is having demonstrated that TG can be applied in a regular and precise way in the

242 registration of paediatric cancers, fostering and facilitating collaboration between international and national paediatric

243 and registries cancer societies/associations. Wide adoption of these guidelines in registries will ease international

244 comparative incidence and outcome studies. Finally, the adoption of the TG by the majority of registries will definitely

245 improve the interpretation of survival data and help find the more appropriate solutions for improving the outcome of

246 childhood cancers.

247

250 **Conflict of interest statement**

251 The authors declared no conflicts of interest.

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258 **Data availability statement**

259 Grouped data are available from the corresponding author

260

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342   Comparisons of Clinical Demographics and Outcomes in the SIOP Wilms Tumour 2001 Trial and Study (2002-

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344

345   **Figure Legend:**

346   Figure 1: Neuroblastoma (A) and Wilms tumours (B) by Toronto stage by European country (indicated by letter)