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REGULAR ARTICLE

# Single-centre study reports a 84% five-year overall survival rate for paediatric solid tumours

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## ABSTRACT

**Aim:** We investigated the characteristics and outcome of paediatric patients with solid tumours diagnosed and treated at the Tampere University Hospital, one of the five tertiary referral centres in Finland, for children and adolescents with malignancies.

**Methods:** This retrospective cohort study collected data from hospital medical records on survival, diagnosis, age, sex, tumour size and stage at diagnosis. We also observed the disease recurrence and use of autologous haematopoietic stem cell transplantation. Data analyses were carried out with the Kaplan–Meier method, various nonparametric and parametric tests, and Cox regression modelling.

**Results:** Between 1987 and May 2015, 424 children (59% boys), with a median age of 6.4 (IQR 2.5–11.8) years at diagnosis, were diagnosed and followed up for a median of 7.5 (range 0-27.9) years. Central nervous system (CNS) tumours were the most common (38%), followed by lymphomas (19%), soft tissue sarcomas (10%), renal tumours (9%) and neuroblastomas (9%). The five-year overall survival rate of all solid tumour patients was 84% (95% CI, 81–88%), 82% (95% CI, 76–89%) for CNS and 85% (95% CI, 80-90%) for non-CNS tumours. Advanced tumour stage at diagnosis predicted a poor prognosis.

**Conclusion:** The treatment results in our study are comparable with those previously published. A comprehensive local database allows for a timely follow-up of the characteristics and quality of treatment of childhood malignancies.

## INTRODUCTION

Cancer in childhood and adolescence is a rare event and currently about 19 of every 100,000 will receive a cancer diagnosis in Finland before 20 years of age (1). Leukaemias are the most common paediatric cancers followed by central nervous system (CNS) and other solid tumours. There is a remarkable spectrum of various histopathological diagnoses for solid tumours in childhood, and the advent of modern genetic diagnostic methods has further increased the number of disease subtypes. The survival of childhood malignancies has dramatically improved since the 1950s, but almost plateaued over the last two decades (2–4). Data collected from the Finnish Cancer Registry showed a five-year survival rate of all childhood malignancies of 82.1% over the period of 2001–2010 (5). Similar results were reported in our hospital for leukaemias and solid tumours during years 1997–2006 (6). A long-term follow-up study of Finnish patients showed that there has only been a marginal improvement in prognosis over the last decade (5). In a Europe-wide study, the five-year overall survival (OS) of all childhood malignancies was 79.1%, slightly better in the Northern European countries at 81.2% (4).

There is remarkable variation in the survival rates between, and within, the solid tumour diagnostic entities. For example, the prognosis of Hodgkin's lymphoma is excellent at around 95%, whereas osteosarcomas exhibit less favourable OS rates of approximately 62%. An

**Abbreviations**
CNS, Central nervous system; ICCC, International classification of childhood cancers; OS, Overall survival.

**Key notes**

- This study investigated the characteristics and outcome of 424 paediatric solid tumour patients with a median age of 6.4 years at diagnosis and treated at a tertiary referral centre in Finland.
- Central nervous system (CNS) tumours were the most common (36%), and the five-year average overall survival probability was 84% for all paediatric solid tumours, 82% for CNS and 85% for non-CNS tumours.
- Advanced tumour stage at diagnosis predicted a poor prognosis.

advanced stage at diagnosis is associated with worse survival (7).

We compiled a comprehensive database of childhood solid malignancies treated in the area covered by the Tampere University Hospital, Finland. This database explored further characteristics of the paediatric solid tumours, survival of patients and use of autologous hematopoietic stem cell transplantation. The results were compared with the published literature.

## MATERIALS AND METHODS

A retrospective cohort study was performed at the Department of Paediatrics at Tampere University Hospital, a tertiary referral centre for childhood tumours. The hospital currently serves four counties in Mid-Western Finland with a population of around one million. The study population contained patients aged less than 16 years at diagnosis, diagnosed with a primary solid tumour between 1987 and 29 May 2015 in the centre and followed up until that date or until death. This register-based study was approved by the Pirkanmaa Hospital District Science Centre in accordance with local regulations.

### Data collection

Patient data were retrieved from the medical records of the Tampere University Hospital and placed in a local electronic relational database. The data were frozen for follow-up on 29 May 2015. Although exact tumour staging systems vary, the main principles remain the same, with stages one to three defining a locoregional and stage four a metastatic disease. The main outcome variable of this study, survival time based on the current status or the date of death, was updated from the Population Register Centre. For the explanatory variables, the cancers were first grouped into diagnostic categories according to the International Classification of Childhood Cancers third edition (ICCC-3) (8). This was based on histopathological and microscopic confirmation. Tumour size was measured as the biggest diameter of the tumour.

### Data analysis and statistics

R 3.2.3 software (9) was used for all analyses. All analyses, including the R code, can be obtained at request. No sample size calculations were carried out beforehand with the study being exploratory and descriptive in nature. In all the analyses, patients with missing values and incomplete observations of a particular combination of variables were discarded (without sensitivity analyses of the possible effects). The missing values are detailed in Table 1. All calculated p values are two-sided with confidence intervals of 95%.

Overall survival (OS) rates were estimated using the Kaplan–Meier method and log-rank test without weight in all patients and diagnostic groups, and by stage and autologous hematopoietic stem cell transplantation (auto-HSCT) status. The assumption of similar prospects for early and late diagnosed cases was investigated by comparing cases diagnosed before and after 2000, as well as by Cox regression modelling, and the assumption seemed feasible (Fig. S1). Comparison by auto-HSCT status was further adjusted by age, stage and recurrence status in a Cox regression model to account for confounding by severity.

The relationship between the tumour size and disease stage was tested with the Kruskal–Wallis test, followed by pairwise Mann–Whitney *U*-tests with Bonferroni multiple testing correction. The relationship between tumour size and age was assessed with the Pearson's correlation coefficient and the relationship with sex using the Mann–Whitney *U*-test. Transplantation proportions were estimated with multiple exact binomial confidence intervals. Stage distributions were estimated with simultaneous confidence intervals for multinomial proportions.

## RESULTS

### Clinical characteristics

A total of 424 primary solid tumours were diagnosed in children (59% male) between birth and 15.9 years of age (median 6.4; IQR 2.5–11.8) at the Tampere University Hospital between 1987 and 29 May 2015 (Table 1). Of the 402 patients (95%) with a diagnosis available, 151 (38%) were CNS tumours. Of the 251 non-CNS solid tumours, the largest group was lymphomas, with 77 cases (31% of non-CNS tumours), followed by 40 (16%) soft tissue sarcomas, 37 (15%) renal tumours and 37 (15%) neuroblastomas. We observed a typical age distribution for tumours, including a preponderance of younger patients with renal tumours or neuroblastomas and older patients with bone sarcomas or lymphomas (Table 1).

### Survival of the solid tumour patients

As shown in Figure 1 and Table S1, the prognosis varied markedly between the different tumour types. The median follow-up time for all solid tumours was 7.5 years (range 0-27.9). The overall survival (OS) rate of living at least one year was estimated to be 95% (95% CI, 93-97%) for all tumours, and the five-year OS rate was 84% (95% CI, 81–88%). The CNS tumours that met the ICCC-3 criteria had a median follow-up of 8.1 years, with an OS rate of 82% (95% CI, 76–89%) and a 20-year OS rate of 77% (95% CI, 69–85%). The non-CNS solid tumours had a median follow-up of 7.5 years with a five-year OS rate of 85% (95% CI, 80–89%) and a 20-year OS rate of 83% (95% CI, 78–88%). Of the main ICCC-3 categories, retinoblastomas, lymphomas, renal tumours and germ cell tumours had the most favourable OS. Tumours with the poorest OS were hepatic malignancies, bone tumours and neuroblastomas. Lymphomas were further subdivided, and a high OS of Hodgkin patients was noted with no registered deaths after one year follow-up. Apart from the CNS and germ cell tumours, most events occurred relatively early on during follow-up (Fig. 1).

We compared the prognosis between diagnoses made from 1990–1999 and 2000–2015. The survival estimates remained very similar ($p = 0.875$) (Fig. S1). The unadjusted

 

**Table 1** Frequency cross-tabulation of the data, including missing data, by studied variables and the main childhood solid tumour groups according to the ICCC-3 (8) classification system

| Variable | Value | All | II | III | IV | V | VI | VII | VIII | IX | X | XI | XII | Missing |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | Total | **424** | **77** | **151** | **37** | **12** | **37** | **6** | **10** | **40** | **14** | **14** | **4** | **22** |
| | Boy | **252** | 56 | 91 | 20 | 12 | 24 | 4 | 5 | 20 | 5 | 3 | 1 | 11 |
| | Girl | **172** | 21 | 60 | 17 | 0 | 13 | 2 | 5 | 20 | 9 | 11 | 3 | 11 |
| Age at diagnosis | 0–3 | **146** | 6 | 49 | 27 | 9 | 21 | 4 | 0 | 13 | 7 | 0 | 3 | 7 |
| | 4–7 | **103** | 21 | 46 | 8 | 2 | 13 | 0 | 0 | 6 | 4 | 0 | 1 | 2 |
| | 8–11 | **73** | 20 | 27 | 1 | 0 | 1 | 1 | 3 | 10 | 1 | 3 | 0 | 6 |
| | 12–15 | **102** | 30 | 29 | 1 | 1 | 2 | 1 | 7 | 11 | 2 | 11 | 0 | 7 |
| Year of diagnosis | 1987–1993 | **20** | 4 | 4 | 1 | 3 | 7 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | 1994–2000 | **94** | 20 | 31 | 9 | 3 | 10 | 1 | 2 | 10 | 5 | 1 | 0 | 2 |
| | 2001–2007 | **127** | 20 | 54 | 13 | 0 | 7 | 3 | 2 | 10 | 1 | 5 | 2 | 10 |
| | 2008–2015 | **183** | 33 | 62 | 14 | 6 | 13 | 2 | 6 | 19 | 8 | 8 | 2 | 10 |
| Death status | Alive | **356** | 69 | 120 | 30 | 11 | 32 | 2 | 7 | 34 | 13 | 13 | 4 | 21 |
| | Dead | **68** | 8 | 31 | 7 | 1 | 5 | 4 | 3 | 6 | 1 | 1 | 0 | 1 |
| Death year | 1995–1999 | **7** | 2 | 2 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 2000–2004 | **18** | 3 | 8 | 2 | 0 | 1 | 1 | 0 | 2 | 0 | 0 | 0 | 1 |
| | 2005–2009 | **22** | 2 | 8 | 3 | 0 | 3 | 2 | 0 | 2 | 1 | 1 | 0 | 0 |
| | 2010–2015 | **21** | 1 | 13 | 2 | 0 | 0 | 1 | 2 | 2 | 0 | 0 | 0 | 0 |
| Autologous Stem cell Transplantation | Not done | **376** | 72 | 144 | 25 | 10 | 31 | 6 | 8 | 28 | 13 | 14 | 3 | 22 |
| | Done | **48** | 5 | 7 | 12 | 2 | 6 | 0 | 2 | 12 | 1 | 0 | 1 | 0 |
| Stage at diagnosis | 1 | **164** | 18 | 72 | 9 | 7 | 7 | 2 | 3 | 22 | 5 | 3 | 2 | 14 |
| | 2 | **65** | 20 | 20 | 7 | 0 | 13 | 0 | 0 | 1 | 3 | 1 | 0 | 0 |
| | 3 | **47** | 16 | 16 | 1 | 0 | 4 | 0 | 1 | 3 | 1 | 3 | 1 | 1 |
| | 4 | **71** | 12 | 12 | 18 | 1 | 9 | 3 | 4 | 5 | 3 | 4 | 0 | 0 |
| | Missing | **77** | 11 | 31 | 2 | 4 | 4 | 1 | 2 | 9 | 2 | 3 | 1 | 7 |
| Tumour size (cm) | 0–4 | **137** | 22 | 53 | 18 | 1 | 4 | 0 | 1 | 16 | 6 | 9 | 1 | 6 |
| | 5–9 | **82** | 14 | 31 | 8 | 0 | 10 | 2 | 3 | 5 | 2 | 1 | 1 | 5 |
| | 10–14 | **56** | 12 | 1 | 6 | 0 | 17 | 2 | 2 | 7 | 5 | 1 | 1 | 2 |
| | 15–20 | **19** | 6 | 0 | 2 | 0 | 2 | 2 | 0 | 4 | 1 | 0 | 0 | 2 |
| | Missing | **130** | 23 | 66 | 3 | 11 | 4 | 0 | 4 | 8 | 0 | 3 | 1 | 7 |

2015 only until 2015-05-29.
ICCC-3 codes: II. Lymphomas and reticuloendothelial neoplasms; III. CNS and miscellaneous intracranial and spinal neoplasms; IV. Neuroblastoma and other peripheral nervous cell tumours; V. Retinoblastoma; VI. Renal tumours; VII. Hepatic tumours; VIII. Malignant bone tumours; IX. Soft tissue and other extra-osseous sarcomas; X. Germ cell and trophoblastic tumours and gonad neoplasms; XI. Other malignant epithelial neoplasms and malignant melanomas; XII. Other and unspecified malignant tumours.
Total number of cases shown in bold.

and adjusted (age, auto-HSCT, sex and stage) Cox regression analyses supported virtually the same conclusion (unadjusted HR = 1.02 [95%CI, 0.98–1.06], adjusted HR = 1.05 [95%CI, 0.99–1.11]).

The small number of cases in individual ICCC-3 categories did not permit further analyses on predictive factors.

### Disease stage and tumour size at diagnosis

Of the 212 patients with non-CNS solid tumours and staging data available, 37% had a stage one, 21% had stage two, 14% had stage three and 28% had stage four disease (Table 1 and Fig. S2). The staging and survival data were available for 209 non-CNS tumours showing a survival significantly worse for children with an advanced stage at diagnosis. The five-year survival probability decreased by the stage of the tumour: stage one 97% (95% CI, 94–100%), stage two 100%, stage three 90% (95% CI, 80-100%) and stage four 60% (95% CI, 48–74%) ($p < 0.001$) (Fig. 2A and Table S1). This was demonstrated further by the 35 neuroblastoma cases with staging data available, where all seven deaths occurred in stage four cases ($p = 0.037$) (Fig. 2B). In an unadjusted Cox regression analysis of the non-CNS tumour patients, patients having a stage four disease at diagnosis as compared to stages 1–3 had an increased risk for death by HR 12.6 (95% CI, 5.1–30.9).

Of the 169 non-CNS tumour patients with stage and tumour size data, the patients with a stage one disease at diagnosis had tumours significantly smaller than those with a more advanced disease ($p < 0.001$) (Fig. 2C). However, there was no correlation between the tumour size and age at diagnosis, and tumour sizes were very similar between the sexes (Fig. S3).

### Autologous haematopoietic stem cell rescue in solid tumours

Autologous haematopoietic stem cell rescue was performed on 42 patients during the study period in Tampere University Hospital (six were carried out elsewhere), and we

 

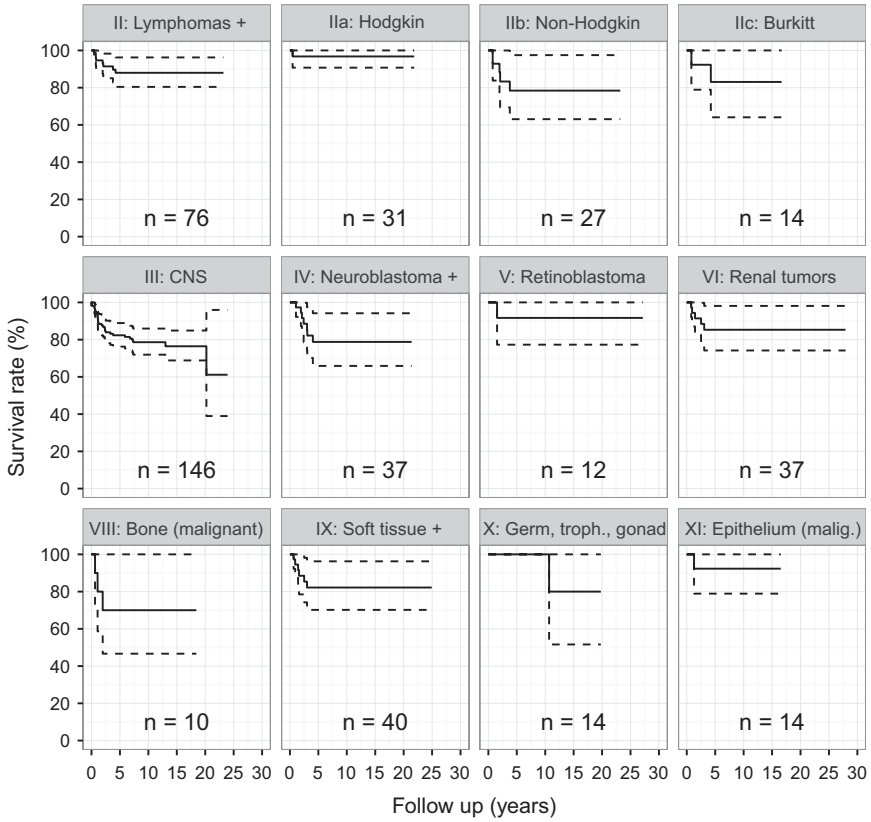


**Figure 1** Overall survival rates (Kaplan–Meier) with 95% confidence intervals (dashed lines) and the number of childhood solid tumour patients, by the diagnostic classes according to the ICCC-3 (8) classification system. Classes that included less than 10 patients are not shown.

examined the incidence of transplants for the 402 patients available. This showed that transplants occurred in 12 (29%; 95% CI, 17–47%) of the patients with soft tissue sarcomas, 11 (31%; 95% CI, 16–48%) with neuroblastomas and six (4%; 95% CI, 1.5–8.5%) with CNS tumours (Fig. S4A). By stratified Kaplan–Meier analysis, the survival of patients who received high-dose chemotherapy and stem cell rescue was worse for both the CNS ($p = 0.013$) and non-CNS solid tumours ($p < 0.001$) as compared to those with conventional chemotherapy (Table S1). However, when adjusted by age, stage and recurrence status, HR was nonsignificant at 1.4 (95% CI, 0.6–3.1) for patients with auto-HSCT (Fig. S4B).

## DISCUSSION

We studied the characteristics and survival of paediatric solid tumour patients diagnosed at the Tampere University Hospital, by generating a local electronic database on childhood haematology and oncology patients and collecting the key variables on all paediatric solid tumours diagnosed in our clinic. Our results showed an overall five-year survival rate of 84% (95% CI, 81–88%) for patients with paediatric solid tumours. We demonstrated that advanced disease stage at diagnosis was associated with worse prognosis, especially for the first five years after diagnosis, as shown previously (7,10).

The treatment results in our series were encouraging. The survival rates in our cohort are comparable with two recent studies from Europe and Finland, as shown in Figure 3, and other recent survival analyses (4,5,7,10,11). As an example, patients with Hodgkin's lymphoma fared extremely well with an OS of 97%, whereas those with a non-Hodgkin lymphoma had slightly poorer outcome as compared to a large European study (4).

Detailed comparisons in some of the diagnostic groups and all of the subgroups could not be performed due to a limited number of cases. An advanced disease stage was associated with a markedly worse prognosis, and this was particularly evident in neuroblastoma with all the deceased patients having a metastatic disease at diagnosis. Most events occurred within five years of diagnosis, implying that children surviving beyond the five years can anticipate a close to similar survival as children in the general population (12). Yet, even though the tumour size reflected the stage of disease, it was not associated with patient age.

During the study period, 42 patients with solid tumours received high-dose chemotherapy and autologous haematopoietic stem cell rescue in our hospital. The second most common indication was metastatic neuroblastoma, a well-established indication. High-dose chemotherapy was also administered to patients with soft tissue and bone sarcomas and CNS tumours, according to investigational

 

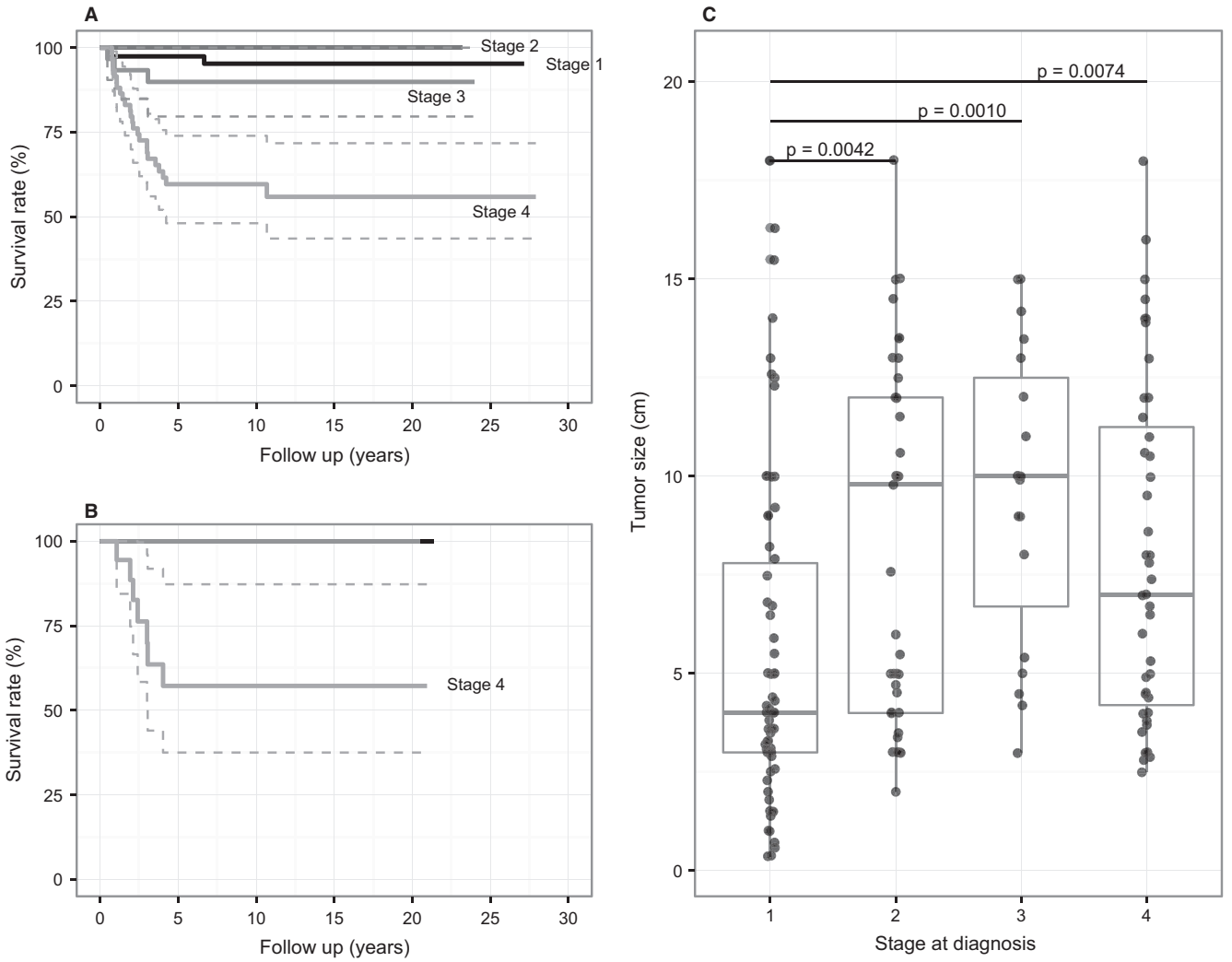


**Figure 2** (A) Survival rates (Kaplan–Meier) of non-CNS solid tumour patients and (B) neuroblastoma patients, by stage at diagnosis. In (A), 95% confidence intervals (dashed lines) are shown only for stage three and stage four groups (p = 3.5e-11 given null hypothesis of identical survival in all stage groups). In (B), 95% confidence interval shown only for stage four group (p = 0.037 given null hypothesis of identical survival in all stage groups). (C) Tumour size (cm) by stage at diagnosis in non-CNS solid tumour patients.

protocols or salvage (13,14). Although the use of high-dose chemotherapy with stem cell rescue is controversial in most paediatric cancers, diseases such as high-risk neuroblastoma or Hodgkin's disease have demonstrated improved outcomes in clinical trials (2,15–17). In our series, after adjusting for recurrence, age and stage, there was no difference between patients receiving either high-dose chemo and auto-HSCT or conventional chemotherapy.

One of the strengths of our study was that the data were collected from a single-centre as population-based, and the diagnostics were based on microscopic and histopathological confirmation. Follow-up was extensive and complete, lasting for up to 28 years, and the proportion of unspecified tumours was low. Study limitations include a low number of cases in some of the main diagnostic groups excluding a detailed subgroup analysis, and some missing values. It should also be noted that the number of cases from the 1980s was low probably reflecting inadequacies in data collection at that time. During the study period, the treatment protocols and practices, as well as diagnosis and even possibly aetiological factors, have changed. Yet, we did not detect any significant change in survival rates between the different time periods.

Routinely updated medical databases are beneficial in patient care and in the follow-up of the quality of care. The benefits will increase as data collection and analytical techniques and technology become better and more available, and data from various sources are pooled together. In future, we plan to expand our database to include laboratory values and treatment side effects to obtain a more comprehensive view on the diseases, their treatment and outcome at our institution.

 

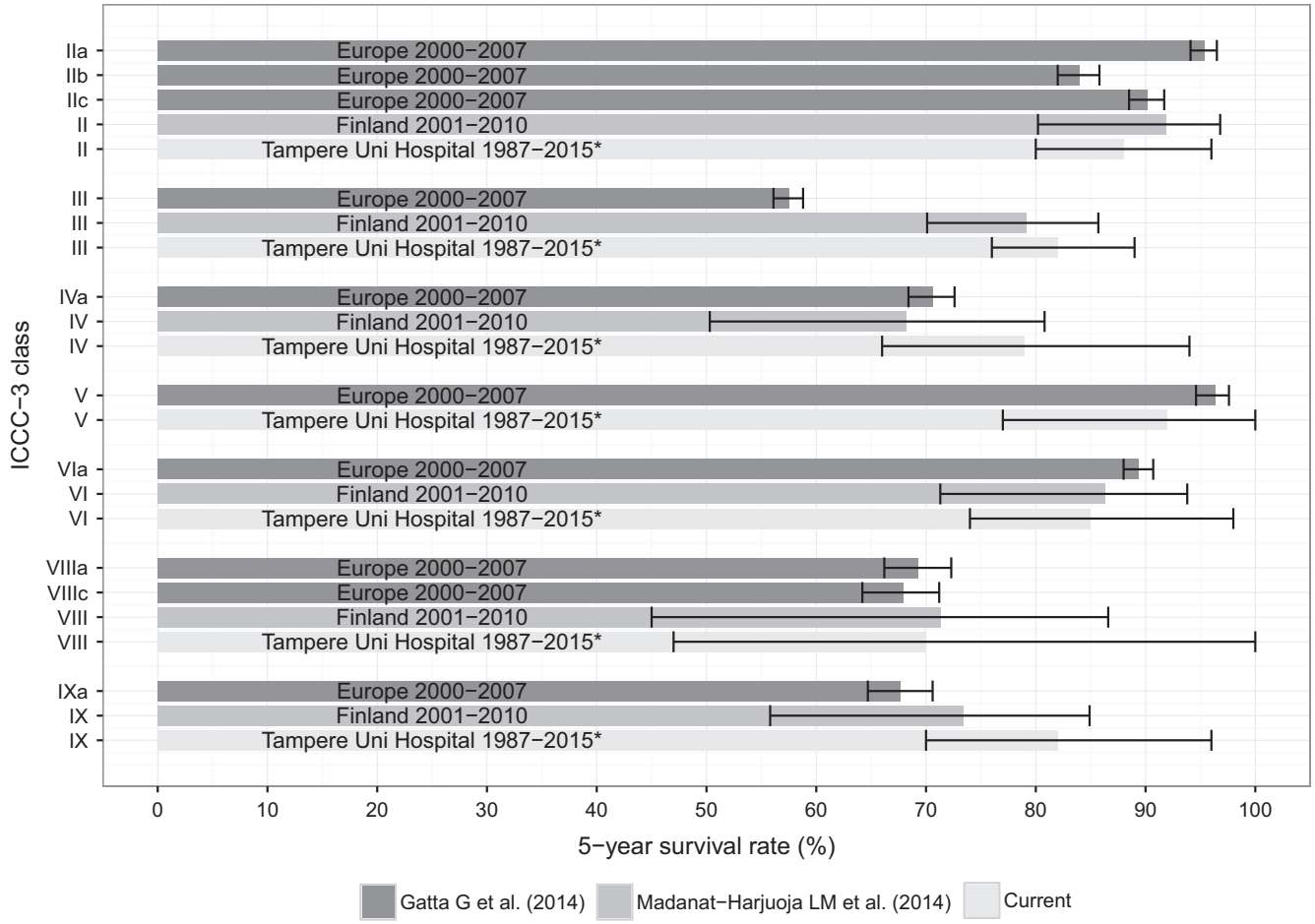


**Figure 3** (A) Five-year survival rate estimates of the current study in the context of estimates from two other studies: a European study by Gatta et al. (4) and a Finnish study by Madanat-Harjuoja et al. (5).

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**CONFLICT OF INTEREST**

The authors have no conflict of interests to disclose.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Figure S1** Survival rates (Kaplan-Meier) of childhood solid tumour patients diagnosed in two different time periods (1990–1999 vs. 2000–2015) (p = 0.875).

**Figure S2** Proportions of patients in each stage category at diagnosis of a childhood solid tumor classified according to the ICCC-3 classification system, with 95% confidence intervals and number of patients.

**Figure S3.** Tumor size distributions, tumor sizes by sex, and tumour sizes by age, in central nervous system (CNS) tumors and non-CNS tumors. Difference in tumor size between boys and girls was −0.9–1.5 cm (95% CI) in non-CNS and 0.65–1 cm (95% CI) in CNS-tumors. Pearson correlation between tumor size and age was −0.13–0.15 (95% CI) in non-CNS and -0.41 to (−0.004) cm (95% CI) in CNS-tumors.

**Figure S4** (A) Proportion of patients (n = 42) with autologous hematologic stem cell transplants (auto-HSCT) by solid tumour classes according to the ICCC-3 (8) classification system, with 95% confidence intervals. Note that we left out patients (n = 6) to whom auto-HSCT was performed outside our hospital. (B) Predicted survival rates for stage 4 patients of median age with a recurrence by auto-HSCT with 95% confidence intervals (left), and the hazard ratio coefficients of the fitted Cox regression model with 95% confidence intervals (right).

**Table S1** Tabulation of all of the survival fit (Kaplan-Meier) results at one, five, 10 and 20 years of follow up, with 95% confidence intervals. Empty cell denotes that there are no observations and thus estimation is not possible with this model, auto-HSCT denotes autologous hematologic stem cell transplantation and ICCC3 classification system (8) of childhood tumours. Note that the number of patients in the analyses differ slightly from Table 1 because the modeling method removes observations with identical follow up time.

 