Review

What can we learn from geographical comparisons of childhood cancer survival?

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With improvements in treatment for childhood cancer, comparisons of survival rates between countries have become important to inform future health policies and treatment strategies. Population-based cancer registry data are viewed as the gold standard for such comparisons, but even these have potential confounding factors. Here, we review the interpretation of recent geographical comparisons of childhood cancer survival from the viewpoint of the British Isles, a region with a 45-year record of national population-based cancer registration and a national childhood cancer clinical trials organisation in place for nearly 30 years. Using national data on referral patterns to tertiary paediatric oncology centres, we explore some of the reasons for lower survival rates in the past for some tumour groups and anticipate continued improvement in the next decade. Participation in international clinical trials coincided with rapid gains in survival for hepatoblastoma. This exemplifies the potential benefits of international collaborative clinical research, particularly for rare subgroups.

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Successful treatment of childhood cancer relies on many factors, some of which are inherent to each tumour’s biology but some of which can be more readily influenced, such as early recognition of concerning symptoms by families and physicians, referral practices and the availability and implementation of optimal, usually standardised, treatment protocols. Survival from childhood cancer in the UK has been the subject of international comparisons since the EUROCARE studies in the 1990s (Coebergh et al, 2001; Terracini et al, 2001). Most recently, interregional comparisons of both incidence and survival across Europe have been made using the Automated Childhood Cancer Information System (ACCIS) (Steliarova-Foucher et al, 2004). In this study, the regions were defined largely according to UN definitions. As the UK and Republic of Ireland have national population-based cancer registration and contributed large numbers of cases, their data were analysed and presented as a single group under the heading of ‘British Isles’ (BI), separately from the North European region (Pritchard-Jones et al, 2006). This allows comparisons of the basic demographics and outcome for childhood cancer treatment in the BI to be made with other European regions. Although such comparisons may be useful in assessing the effectiveness of cancer services for children, they also raise questions for those subgroups where outcomes are significantly different from the European average. We consider here possible reasons for these differences, particularly whether they are more likely to be attributable to differences in disease occurrence or patterns of care or to artefacts arising from variations in cancer registry practice across Europe. In the ACCIS analyses, the most recent year of diagnosis for most of the BI was 1995 (Steliarova-Foucher et al, 2006), but the results are also discussed in the context of trends in survival in Great Britain up to 2000 and rates of referral to paediatric oncology centres up to 2002.

Before drawing any conclusions from these analyses, one must take into consideration the comparability of the data sources. Comparability issues were considered carefully in deciding which registry data should be included in the ACCIS analyses. Cancer registration is a complex process that relies on comprehensive access to hospital and population records, however, and comparability is not yet perfect owing to national variations in registration practices and access to personal data (Pritchard-Jones et al, 2006; Steliarova-Foucher et al, 2006). For example, incidence and survival figures in registries without access to national mortality databases (as in Germany, France, Netherlands, Italy and Spain) may overestimate survival owing to incomplete follow-up for vital status (Steliarova-Foucher et al, 2006). The data for the BI suffer from this, as legislation permits linkage to databases of identifiable deceased individuals. The ACCIS analyses refer to all diagnoses in the International Classification of Childhood Cancer (Kramarova and Stiller, 1996), that is, all malignant neoplasms and most types of non-malignant intracranial and intraspinal tumours. Although the latter are collected routinely by most cancer registries, there are some variations between registries and hence also between geographical regions, whose implications for interpretation of the results are discussed below.

In the most recent period of the ACCIS analysis (1988–1997), observed overall 5-year survival for 49,651 children aged under 15 years grouped into the five European regions was 72% (Sankila et al, 2006). Observed survival was used in place of relative
survival, as competing causes of death are rare in children in Western populations and relative survival would exceed observed survival by less than one percentage point. For comparison, the 5-year relative survival was 75% in the USA for patients diagnosed in 1985–1999 (Ries et al, 2003). Observed survival ranged from 77% in the North, through 75% in the West, 72% in the South, 71% in the BI to 62% in the East (Sankila et al, 2006). The survival curves tested by log rank were significantly different for the BI compared individually with North, West or East, but were not distinguishable from survival in the South. For this analysis, the regions included data from the following countries: North (Denmark, Iceland, Finland, Norway), West (France, Germany (East and West 1991–1997; former West Germany only 1988–1990), Netherlands, Switzerland), South (Italy, Malta, Slovenia, Spain), BI (Ireland, England, Northern Ireland, Scotland, Wales) and East (Belarus, Estonia, Hungary, Slovakia). Trends in survival were analysed over the 20-year period 1978–1997 with some slight differences in the regional data sets: BI (England, Scotland and Wales), East (Estonia, Hungary, Slovakia, former East Germany, 1978–1987), South (Italy, Slovenia, Spain) (Magnani et al, 2006) (Figure 1). The relative ranking of regions did not alter over this longer study period. Highly significant increases in observed survival were seen in all European regions, with the most rapid rise in the East. For all neoplasms, the BI had a 5-year survival of 74% in the most recent period, 1993–97 (Magnani et al, 2006). Survival has continued to increase, reaching 77% in Great Britain (which accounts for about 90% of cases in the BI) during 1996–2000 (Figure 2) (Stiller, 2007). The reported survival differences between the BI and some other European regions are small in absolute terms. Some of this variation may be artefactual due to several possible factors. First, it should be noted that the BI had the lowest incidence rates in Europe for all childhood cancers combined. The age-standardised rate was 131.1 per million compared with 138.5 per million for Europe as a whole with the highest rate of 160.1 per million in the North (Stiller et al, 2006a). The deficit was found among boys and girls at all ages throughout childhood. It was most marked in the first year of life, with more than half of the difference from the European average being accounted for by the relatively low incidence of neuroblastoma among infants (Stiller et al, 2006a). Incidence rates may influence survival in several ways. For example, survival will increase if there is ‘overdiagnosis’ of cases with a very favourable prognosis that may not otherwise have presented clinically, as has been observed for neuroblastoma (Spix et al, 2006). Variations in diagnostic and registration practices for brain tumours may contribute to higher survival in those regions covered by registries with a higher total incidence resulting from inclusion of a higher proportion of non-malignant cases (Peris-Bonet et al, 2006).

The significance of comparisons of survival among North, South, West and BI for the 12 main groups and the principal subgroups of childhood cancers is weakened by their ‘post hoc’ nature and the fact that the large number of comparisons means that some significant results would be expected to arise by chance. In general, the highest survival figures were often observed in the North. Differences were seen between the BI and the region(s) with highest 5-year survival for sympathetic nervous system tumours, renal tumours and soft tissue sarcomas (Pastore et al, 2006a,b; Spix et al, 2006). Differences in observed survival were also noted for the following subgroups: neuroblastoma, Wilms tumour, acute lymphoblastic leukaemia (ALL), osteosarcoma, primitive neuro-ectodermal tumours/medulloblastoma and ‘glioma-related’ brain tumours, although the composition of this last subgroup is too heterogeneous for meaningful comparison, as explained below (Cobergh et al, 2006; Peris-Bonet et al, 2006; Pastore et al, 2006a; Spix et al, 2006; Stiller et al, 2006b). Despite these limitations, possible reasons for these potential differences in certain tumour groups merit further consideration, as they may be informative in stimulating assessment of factors with the potential to influence effectiveness of care.

For neuroblastoma, it has been recognised previously that the BI has a lower total incidence that includes a relatively high proportion of older children with disseminated disease, compared with some other Western European countries (Powell et al, 1998). This pattern of presentation may be partially explained by the influence of screening programmes and differences in the use of diagnostic ultrasound in paediatric primary care in other European countries and may, to some extent, explain the lower survival in Great Britain during 1988–1995. Survival has improved consistently since this period (Figure 3). This improvement is not easily explained as the same clinical trial for the major subgroup of children with stage 4 disease (ENSG V, 1990–1999) ran throughout both periods. Further analysis would require data that are beyond the current scope of cancer registries, such as participation rates in randomised clinical trials, where the more intensive experimental arm subsequently showed a survival benefit.

Survival for children with renal tumours in the BI, comprising mainly Wilms tumours, remained static in the BI during the ACCIS study period and was similar to rates in the South, but inferior to rates in the North and West (Pastore et al, 2006a). This overall picture suggesting no change is confounded by an unexplained fall in survival in the early 1990s compared with the late 1980s (Stiller, 2007). Overall survival has subsequently improved markedly,
which may be partially attributable to the introduction of a national strategy for treatment of relapsed Wilms tumour in the late 1990s (Figure 3).

Geographical comparisons of survival from soft tissue sarcomas are complicated by the fact that this diagnostic group encompasses a diverse collection of histological entities with widely differing prognosis, together with the possibility that terminology and registration practice varied systematically between regions. Most notably, the North had the highest incidence and survival rates for the subgroup of fibrosarcoma and allied tumours, and the possibility that this was attributable to inclusion of some cases of non-malignant conditions such as fibromatosis could not be excluded (Pastore et al, 2006). The subgroup of ‘Other specified soft tissue sarcomas’, for which the North and South regions had markedly higher survival rates than the BI and West, is also very heterogeneous and includes tumour types with widely differing survival. The difference in survival between the BI and the North was twice as large for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children.

The differences in survival between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children. The differences between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children. The differences between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children. The differences between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children. The differences between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children. The differences between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children. The differences between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children. The differences between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children. The differences between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children. The differences between the BI and the North were marked for all soft tissue sarcomas combined, as it was for rhabdomyosarcoma, the well-defined and least heterogeneous subgroup in European children.
Table 1 Percentage of children with cancer in Great Britain initially referred to a CCLG (formerly UKCCSG) centre by ICC-3 main diagnostic group and for all groups combined

| Diagnostic groups       | 1988–1995 | 1996–2000 | 2001–2002 |
|-------------------------|-----------|-----------|-----------|
| I Leukaemia             | 87        | 93        | 95        |
| II Lymphoma             | 86        | 91        | 94        |
| III CNS                 | 65        | 85        | 85        |
| IV Sympathetic Nervous system | 96    | 98        | 98        |
| V Retinoblastoma        | 88        | 93        | 91        |
| VI Renal tumours        | 94        | 98        | 99        |
| VII Hepatic tumours     | 88        | 90        | 97        |
| VIII Bone tumours       | 74        | 94        | 92        |
| IX Soft tissue sarcoma  | 85        | 90        | 85        |
| X Germ cell and gonadal | 77        | 82        | 90        |
| XI Melanoma and other carcinoma | 23 | 36        | 35        |
| XII Other               | 11        | 35        | 36        |
| All cancers combined (I–XII) | 79    | 88        | 90        |

Results are given for the period corresponding to the ACCIS analyses (data for England and Wales in the geographical comparison of survival was cutoff at 1995, (Sankila et al, 2006), the more recent quinquennium and the most recent period (2001 – 2002) for which registration data are virtually complete. Source: National Registry of Childhood Tumours, Oxford.

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