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Original Research

Persisting inequalities in survival patterns of childhood neuroblastoma in Southern and Eastern Europe and the effect of socio-economic development compared with those of the US

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Abstract ***Aim:*** Neuroblastoma outcomes vary with disease characteristics, healthcare delivery and socio-economic indicators. We assessed survival patterns and prognostic factors for patients with neuroblastoma in 11 Southern and Eastern European (SEE) countries versus those in the US, including—for the first time—the Nationwide Registry for Childhood Hematological Malignancies and Solid Tumours (NARECHEM-ST)/Greece.
Methods: Overall survival (OS) was calculated in 13 collaborating SEE childhood cancer registries (1829 cases, ~1990–2016) and Surveillance, Epidemiology, and End Results (SEER), US (3072 cases, 1990–2012); Kaplan–Meier curves were used along with multivariable Cox regression models assessing the effect of age, gender, primary tumour site, histology, Human Development Index (HDI) and place of residence (urban/rural) on survival.
Results: The 5-year OS rates varied widely among the SEE countries (Ukraine: 45%, Poland: 81%) with the overall SEE rate (59%) being significantly lower than in SEER (77%; $p < 0.001$). In the common registration period within SEE (2000–2008), no temporal trend was noted as opposed to a significant increase in SEER. Age >12 months (hazard ratio [HR]: 2.8–4.7 in subsequent age groups), male gender (HR: 1.1), residence in rural areas (HR: 1.3), living in high (HR: 2.2) or medium (HR: 2.4) HDI countries and specific primary tumour location were associated with worse outcome; conversely, ganglioneuroblastoma subtype (HR: 0.28) was associated with higher survival rate.
Conclusions: Allowing for the disease profile, children with neuroblastoma in SEE, especially those in rural areas and lower HDI countries, fare worse than patients in the US, mainly during the early years after diagnosis; this may be attributed to presumably modifiable socio-economic and healthcare system performance differentials warranting further research.

1. Introduction

Neuroblastoma and its variant ganglioneuro blastoma are the most common extracranial solid tumours in children representing 3–8% of childhood malignancies [1,2]. The median age at diagnosis is between 16 and 24 months with a peak occurrence in infancy [3–5] and a significantly higher reported incidence in developed countries [6]. Outcomes range from spontaneous regression to refractory disease. Prognosis varies with age, stage and histological and molecular characteristics [7]. Specifically, amplification of MYC-N oncogene (30% of cases) [1] and numerical and segmental chromosomal abnormalities are common genetic aberrations associated with advanced stage and treatment failure [7]. Treatment depends on the level of projected risk at diagnosis, with overall survival (OS) ranging from >95% for low-risk patients to <40% for those presenting at an advanced stage [8]. Significant inequalities in the outcome of neuroblastoma have been described within Europe, where the OS ranges from 62% (Eastern Europe) to 80% (Northern Europe) [9]. Discrepancies in childhood cancer survival have been linked to socio-economic differentials, urban residence and the Human Development Index (HDI) which is a summary measure of average achievement of a country's population in three areas: life expectancy, education and per capita income indicators [10–14].

The aim of the present study was to calculate adjusted OS and time trends over the last decades among children with neuroblastoma in a network of 13 registries operating in 11 Southern and Eastern European countries (SEE), including, for the first time, the Nationwide Registry for Childhood Hematological Malignancies and Solid Tumours (NARECHEM-ST) in Greece. Comparison of epidemiological patterns with those derived from the publicly available Surveillance, Epidemiology, and End Results (SEER) database was also undertaken to identify possible risk factors and differences in the participating SEE