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Survival from teenage and young adult cancer in northern England, 1968 – 2008

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Abstract

Background: Although cancer is relatively rare in teenagers and young adults (TYAs) aged 15 – 24 years, it is a major cause of death in this age-group. This study investigated survival trends in TYA cancer diagnosed in northern England, 1968 – 2008.

Methods: Five-year survival was analysed using Kaplan-Meier estimation for four successive time periods. Cox regression analysis was used to investigate associations with demographic factors.

Results: The study included 2987 cases (1634 males, 1353 females). Five-year survival for all patients with cancer improved greatly from 46% in 1968 – 1977 to 84% in 1998 – 2008 ($P<0.001$), for patients with leukaemia from 2% to 71% ($P<0.001$), lymphoma from 66% to 86% ($P<0.001$), central nervous system tumours from 53% to 84% ($P<0.001$), bone tumours from 29% to 72% ($P<0.001$), germ cell tumours from 39% to 94% ($P<0.001$), melanoma and skin cancer from 64% to 100% ($P<0.001$) and carcinomas from 48% to 80% ($P<0.001$). Cox analysis showed that for all patients with cancer, survival was better for females than males (HR = 0.83; 95% CI 0.74 – 0.94, $P<0.001$), for patients aged 20 – 24 years compared with those aged 15 – 19 years (HR = 0.84; 95% CI 0.75 – 0.94, $P=0.002$), but survival was worse for patients who resided in more deprived areas (HR = 1.06; 95% CI 1.01 – 1.11, $P=0.025$).

Conclusion: There have been large improvements in TYA cancer survival in northern England over the last four decades. Future work should determine factors that could lead to even better survival, including possible links with delayed diagnosis.

Introduction

Although cancer is relatively rare in teenagers and young adults (TYAs) aged 15 – 24 years, it is a major cause of death in this age group [1]. Cancer accounts for 8% of all deaths in TYA males and 14% of all deaths in TYA females and it is the fourth and the second most common cause of death in TYA males and females respectively in the UK. Between 2008 and 2010, there was an average of 313 TYA cancer deaths per year in the UK [2-5]. Cancer in TYAs is different from cancer in children (aged 0 – 14 years) and in older adults (aged 25+ years) as it is a mix of late onset paediatric cancers, early onset adult cancers and cancers that have a peak incidence in this age-group. The most frequent cancers in this age-group are lymphomas, carcinomas, germ cell tumours, leukaemia, bone and soft tissue sarcomas and central nervous system tumours (CNS) [6].

It has been acknowledged that TYAs with cancer have specific psychological, social and developmental needs that may necessitate access to specialist TYA care [7]. TYAs with cancers have poorer outcomes (worse survival) compared to children with biologically similar cancers. This may be due to limited access to clinical trials and/or delay in diagnosis or differences in tumour biology [8,9]. However, survival from TYA cancers diagnosed in England has improved consistently over time between 1979 and 2003 [10]. Five-year survival for all European TYA cancers combined, diagnosed during 1995 – 2002, was 87% [11]. Survival from TYA cancer in England improved substantially with five-year relative survival reaching 76% for all cancer cases diagnosed 1996 – 2001[10]. A previous study from the former Northern Region of England examined survival in TYA diagnosed during 1968 – 1997 and reported significant improvements [12].

The aim of the present study was to investigate survival for cancer in TYAs (aged 15 – 24 years) diagnosed during the period 1968 – 2008, and registered by the population-based

Northern Region Young Persons' Malignant disease Registry (NRYPMDR). The study examined patterns and trends in survival, updating the previously published analysis and also presents gender-specific results.

Materials and methods

All cases aged 15 – 24 years, diagnosed with a primary malignancy during the period 1968 – 2008 were obtained from the NRYPM DR. The NRYPM DR is a specialist registry, established in 1968, covering the counties of Northumberland, Tyne and Wear, Durham, Teesside, and Cumbria (excluding Barrow-in-Furness). All cases of cancer in the region, diagnosed in 0 – 24 year olds, are notified to the registry. Cases are identified from multiple sources. Consultants throughout the region notify the registry of any malignancies in this age-group. Data are periodically cross-checked with regional and national cancer registries. The registry has a high level of overall completeness and ascertainment, estimated to be more than 98%, with less than 2% lost to follow-up over the entire study period. Follow-up was achieved by regular checking of death certificates and hospital admission data [13]. The morphology-based classification scheme for cancers in TYAs aged 15 – 24 was used [14].

Statistical analysis

Survival at five-years was analysed using Kaplan-Meier estimation, for each diagnostic group, within four successive sub-periods: 1968 – 1977, 1978 – 1987, 1988 – 1997, 1998 – 2008 [15]. Unadjusted trends in survival for each diagnostic group were assessed using Cox regression. The endpoint of interest was death from any cause, with date of diagnosis taken to be the time of origin. The NRYPM DR attempts to obtain comprehensive long-term follow-up on all childhood, teenage and young adult patients and was mostly complete until 31st December 2012.

Cox proportional hazards regression analysis was used to model the probability of survival in relation to age-group at diagnosis (15 – 19 and 20 – 24 years), gender, sub-period of diagnosis (1968 – 1977, 1978 – 1987, 1988 – 1997 and 1998 – 2008), area-level socio-economic deprivation quintiles, and area-level population density for all diagnostic groups

and subgroups with greater than 45 cases for the entire follow up period. Simpler models, with sub-period of diagnosis as both a continuous and a non-linear variable were fitted to assess the trends over time in survival. The significance of each covariate in the model was assessed using the partial likelihood ratio test. Non-nested models were compared using the Akaike's Information Criterion [16]. Hazard ratios (HRs) of variables were retained in the model only if they contributed significantly to the overall model fit. The proportional hazards assumption was tested by examining Schoenfeld residuals and only models that met the assumption were included in the results [17].

Townsend deprivation score for the census ward of residence was used to divide cases into five groups, from the most affluent to the most deprived [18]. Townsend scores were based on 1971, 1981, 1991 and 2001 censuses estimated for 2001 census ward geography [19,20]. Population density for each electoral ward was calculated by dividing the population by the area. Wards were classified according to tertile of population density (for the period 1968 – 1985: low population density 2 – 1068 persons per km²; medium population density 1077 – 3159 persons per km²; high population density 3211 – 11357 persons per km²; for the period 1986 – 1995: low 2 – 1058 persons per km²; medium 1072 – 3130 persons per km²; high 3192 – 10682 persons per km²; and for the period 1996 – 2008: low 2 – 1056 persons per km²; medium 1077 – 3189 persons per km²; high 3194–8882 persons per km²). The ward population density figures for the periods 1968 – 1985, 1986 – 1995 and 1996 – 2008 were based respectively on the 1981, 1991 and 2001 censuses estimated for 2001 census ward geography [19,20]. All statistical tests were two-sided and statistical significance was taken to be $P < 0.05$ in all analyses. Stata version 12 was used for the statistical analysis.

Results

The study included a total of 2,987 TYA cancer cases, diagnosed during the period 1968 – 2008 (1,634 males and 1,353 females). Five-year survival by sub-period of diagnosis, for the diagnostic groups and subgroups is given in Table I and for males, females, and by age-group 15 – 19 and 20 – 24 years in Supplementary Table I, Supplementary Table II, Supplementary Table III and Supplementary Table IV respectively. Survival for all cancers increased significantly over the study period ($P < 0.001$) from a five-year survival of 46% for the sub-period 1968 – 1977 to 62% for 1978 – 1987, 73% for 1988 – 1997 and 84% for 1998 – 2008 (Figure 1). For all leukaemia and lymphoma combined, survival increased from 44% to 67%, 70% and 80% for the four sub-periods respectively ($P < 0.001$). Also, survival for solid tumours increased from 47% to 59%, 75% and 86% respectively ($P < 0.001$). Cox regression modelling for all cancers showed that sub-period of diagnosis, gender, age-group and deprivation were significant in the final model ($P < 0.001$, $P = 0.003$, $P = 0.002$ and $P = 0.025$ respectively). Survival was significantly better for females (HR = 0.83; 95% CI 0.74 – 0.94) compared with males (Figure 2), and better for 20 – 24 years of age (HR = 0.84; 95% CI 0.75 – 0.94) compared with 15 – 19 years of age (Figure 3). After adjustment for these variables, survival was worse the more deprived the Townsend quintile of the patient's residential area at diagnosis (HR = 1.06; 95% CI 1.01 – 1.11).

Including sub-period of diagnosis as a continuous variable, significantly improved the model fits for survival of several groups and subgroups of cancer, the non-linearity assumption was tested and was not significant for most of the groups or subgroups (Table 1). There was no evidence for an effect of area-level residential population density on survival so it was omitted from all final models.

Leukaemia

Survival was very low for leukaemia at the start of the study period but improved markedly, from 2% in the first sub-period to 71% in the fourth sub-period ($P<0.001$) (Supplementary Figure 1). Five-year survival for acute lymphoblastic leukaemia (ALL) increased from 5% in the first sub-period to 38%, 43% and 78% in the second, third and fourth sub-periods ($P<0.001$). Cox modelling showed that age-group and sub-period of diagnosis (as a continuous variable) were significant in the final model for ALL. After adjusting for sub-period of diagnosis, the risk of death was higher for cases aged 20 – 24 years (HR = 1.94; 95% CI 1.28 – 2.93; $P=0.002$) compared with those aged 15 – 19 years. For acute myeloid leukaemia (AML), five-year survival improved markedly from 0% in the first sub-period to 28% and 58% in the second and third sub-periods respectively ($P<0.001$) with no further improvement in the fourth sub-period. Although five-year survival was apparently lower for males diagnosed with AML than for females, reaching 46% and 75% respectively in the fourth sub-period, the difference between the genders was not statistically significant.

Lymphomas

Survival for all lymphomas improved significantly over the study period from 66% in the first sub-period to 86% in the fourth sub-period ($P<0.001$) (Supplementary Figure 2).

Survival for non-Hodgkin lymphoma (NHL) improved significantly. The five-year survival was 32% in the first sub-period and increased to 56%, 64% and 69% in the second, third and fourth sub-periods respectively ($P=0.002$). Cox regression analysis for NHL showed that age-group at diagnosis and sub-period of diagnosis as a continuous variable were significant in the final model ($P=0.001$ and $P=0.04$ respectively). After adjustment for sub-period of diagnosis, the risk of death was lower at ages 20 – 24 years compared with those aged 15 – 19 years (HR = 0.63; 95% CI 0.40 – 0.98). Survival for Hodgkin lymphoma was high from the start of the study period; the five-year survival was 74% in the first sub-period and improved to 93% in the fourth sub-period ($P<0.001$). Cox analysis showed that sub-period and Townsend quintiles of deprivation, as continuous variables,

were significant in the final model ($P<0.001$ and $P=0.002$ respectively). After adjusting for sub-period, survival for Hodgkin lymphoma cases was worse as deprivation increased with HR = 1.25 (95% CI 1.08 – 1.43) per each successive quintile of deprivation ($P=0.002$).

Central nervous system (CNS) tumours

There was a significant increase in survival for all CNS tumours, the five-year survival improved from 53% in the first sub-period to 84% in the last sub-period ($P<0.001$) (Supplementary Figure 3). The most marked increase in five-year survival was for other gliomas from 12% in the first sub-period to 79% in the last sub-period ($P<0.001$). For all cases of astrocytoma, five-year survival improved from 54% in the first sub-period to 76% in the last sub-period ($P=0.005$). For male cases diagnosed with astrocytoma, there was an improvement in five-year survival from 44%, to 62%, 57% and 79% in the first, second, third and fourth sub-periods respectively ($P=0.008$). Also, for female cases of astrocytoma, there has been a fluctuation in five-year survival over the study period which was not significant; this fluctuation in survival may be due to small numbers. There was significant improvement in five-year survival for cases diagnosed with other CNS tumours from 75% in the first sub-period to 94% in the fourth sub-period ($P=0.008$). After adjusting for sub-period, survival for other CNS cases was better as deprivation got worse with HR decreasing by a factor of 0.74 (95% CI 0.59 – 0.94) per each quintile of increasing deprivation ($P=0.014$).

Bone tumours

There was a significant increase in survival for bone tumours especially for osteosarcoma. Five-year survival for all bone tumours increased from 29% in the first sub-period to 30%, 43% and 72% in the second, third and fourth sub-periods respectively ($P<0.001$). Five-year survival for osteosarcoma improved significantly from 35% in the first sub-period to

80% in the fourth sub-period ($P<0.001$) and for Ewing's sarcoma from 0% in the first sub-period to 47% in the fourth sub-period ($P<0.001$).

Soft tissue Sarcoma

Five-year survival for soft tissue sarcoma increased from 33% in the first sub-period to 67% in the last sub-period ($P=0.004$). Cox regression analysis showed that sub-period, as a continuous variable, and gender were significant in the final model ($P<0.001$ and $P=0.023$ respectively). After adjusting for sub-period of diagnosis, TYA males had worse survival than females (HR = 1.69; 95% CI 1.07 – 2.68). However, the proportional hazards assumption was not valid for the final model ($P=0.044$) and therefore this result should be interpreted with caution. For other specified cases of soft tissue sarcoma there was a significant increase in survival from 33% in the first sub-period to 72% in the fourth sub-period ($P=0.007$).

Germ cell tumours

Survival significantly increased for gonadal germ cell tumours from 40% in the first sub-period to 96% in the last sub-period ($P<0.001$). For non-gonadal germ cell tumours, five-year survival improved from 38% in the first sub-period to 78% in the last sub-period ($P=0.037$).

Melanoma and skin cancer

Survival for melanoma improved significantly over the study period from 47% to 100% in the last sub-period ($P<0.001$). For skin cancer, five-year survival remained very high from the start of the study period at 100%.

Carcinomas

Overall five-year survival for carcinomas improved significantly from 48% to 80% in the fourth sub-period ($P < 0.001$). For thyroid carcinoma, five-year survival was very high from the start and reached 100% in the fourth sub-period. For genitourinary tract carcinomas, an observed increase in survival from 61% in the first sub-period to 83% in the fourth sub-period was not statistically significant.

Discussion

This study provides up to date estimates of five-year survival for TYA cancers from a population-based registry from northern England over a forty year period. The population of the former Northern Region is ethnically homogenous with fewer than 2% from minorities [21-23] though a sub-regional analysis would need to account for concentrations of ethnic groups. The overall five-year survival for cancers in TYAs has improved considerably and reached 84% (83% for males and 86% for females) in the latest sub-period (1998 – 2008). The largest improvements in survival were seen for ALL, AML, NHL and bone tumours. The five-year survival for germ cell tumours and carcinomas was very high (more than 90%). Overall, there were continued improvements in survival since our previous study [12]. In the present study we report both overall and gender-specific survival, by morphological diagnostic groupings of cancer appropriate to TYAs.

Improvements in TYA cancer survival reflect continuous advances in treatment and are consistent with those reported from other studies. Five-year survival from all TYA cancer in England, diagnosed 1979 – 2001, was 76% [10], in the EURO CARE study, diagnosed 1995 – 2002, was 87% [11], in the Netherlands at age 15 – 29 years diagnosed 1989 – 2009 was 80 – 82% [24], in Canada at age 15 – 29 years diagnosed 1990 – 2001 was 83% [25] and in the United States (US), at age 15 – 19 and 20 – 24 years diagnosed 2003 – 2009 were 84.5% and 85.5% respectively [26]. However the average annual percent increase in five-year survival from TYA cancer in the US over the last 30 years was much less when compared with this region [27,28].

In England, five-year survival for **patients diagnosed with** ALL, AML, NHL and HL during 1996 – 2000 was 55%, 50%, 72% and 93%, respectively [10]; and for all European TYAs diagnosed 1995 – 2002 was 49.5%, 59.1, 74.4% and 93.1% [11]. Survival for **patients with** AML has markedly improved as more intensive therapy protocols were introduced in the

early 1980s [29]. There have also been significant advances in the molecular characterization of NHL over the last decades enabling the early start of lymphoma specific intensive chemotherapy and most patients can be cured [30].

A previous study from the former Northern Region of England examined survival from childhood cancer diagnosed 1998 – 2005 and reported overall five-year survival of 79% [31]. However, five-year survival remained much lower for TYAs with leukaemia especially AML (71% and 58% versus 81% and 77% in children), NHL (69% versus 83%) and in Ewing's sarcoma (47% versus 73%) [31]. Lower survival rates in adolescents have also been reported from Europe and the USA [9,27,28]. Another previous study from the north of England and Yorkshire of haematological malignancies diagnosed 1990 – 2002, found worse survival at ages 15 – 24, with only 60% of leukaemia patients at these ages entered into clinical trials compared with 92% at ages 0 – 14 years [32]. Similarly poorer survival in TYAs with ALL and AML was reported for Great Britain [10], Europe [11], the Netherlands [24], Canada [25] and the US [28]. There are biological differences that may explain the difference in survival for ALL in children and TYAs [33] as TYA ALL have a distinctive cytogenetic profile [34] and for AML where there is also a difference in biology [32]. Low accrual of TYA into clinical trials may also partly explain poorer outcomes in TYAs [35].

There has been a significant improvement in survival for patients with CNS tumours over the study period especially for astrocytomas, similar to that reported for children [31]. However, no significant improvement in survival for astrocytomas in TYA was reported from the whole of England, 1996 – 2001 [10]. There were also lower survival rates for young adults from Yorkshire with CNS tumours compared to children [36]. Children with astrocytomas have shown marked improvement as these tumours are commonly low-grade [37].

For **patients with** bone tumours there have been marked improvements in five-year survival over the study period. Five-year survival for osteosarcoma and Ewing sarcoma was 49% and 42% for cases diagnosed in England, 1996 – 2001, at ages 13 – 24 years [10], 59.8% and 48% for cases diagnosed 2000 – 2002 in Europe [11] and 58% and 43% for cases aged 0 – 39 years diagnosed 1995 – 2000 in the area comprising northern England and Yorkshire [38]. Five-year survival for osteosarcoma reached 80% in the last sub-period of the present study which is higher than that reported in the whole of England (49%) [10]. However, this result must be interpreted with caution, since study periods are different and numbers in the present study are small. The overall survival for osteosarcoma without clinically evident metastatic disease at diagnosis has increased dramatically over the last 30 years to 65% – 75% [39] but overall survival for cases with metastatic disease at diagnosis was between 10%-50% [40]. A study from Finland reported that ten-year survival for cases of localised osteosarcoma at presentation diagnosed 1991 – 2005 was 73% [41]. The overall survival for osteosarcoma also varied with age and anatomical site [42].

For **patients with** germ cell tumours survival was similar to findings from the whole of England [10]. The treatment and management for germ cell tumours has improved since the 1980s with the introduction of cisplatin based chemotherapy [43]. **Patients with** carcinomas, which constitute the commonest group of cancers in TYAs in this study, showed marked improvement in five-year survival which has also been reported in studies from the whole of England and Europe [10,11].

Cox analysis showed that for all cancers survival was better for females than males, for the older group aged 20 – 24 years and for those living in less deprived areas according to the Townsend deprivation scores. For the specific cancer types and subtypes, there were no significant differences in survival with increasing socioeconomic deprivation, except for

Hodgkin lymphoma. A study from the south of England, reported similar findings for age-group, although with lower five-year survival (69.2% for 15 – 19 year old patients and 78.3% for 20 – 24 year olds diagnosed between 1998 – 2002) [44]. Some studies have shown an association between increasing deprivation and survival for leukaemia and carcinomas in England [10,45]. However, Coleman *et al* have shown that deprivation has a strong influence on cancer survival rates in adults, but much less in children [46]. There were also significant differences in survival for the sub-group comprising other CNS tumours where survival was better for TYAs resident in more deprived areas compared with those from more affluent areas. A similar unexpected association between poorer survival and higher affluence was previously reported for children diagnosed with astrocytoma from the same region [31] and for children and young adults diagnosed with CNS tumours in Yorkshire [33]. These findings may reflect the fact that more deprived areas are mostly urban areas that may be geographically closer to treatment services; however, they should be interpreted with caution and the role of chance cannot be excluded. A limitation of the present study is that it is based on small numbers of total cases, over a forty year period, and this small sample size could have had an impact on the stability of the survival rates with inadequate power to detect associations with survival.

In conclusion, our results indicate that there has been substantial improvement in survival for TYA cancer in the north of England over the last four decades, but it remains lower for leukaemia, NHL and Ewing's sarcoma compared with children. Improvements in survival may generally be attributed to a number of changes in the management and treatment of TYA cancers. These changes are largely due to implementation of national guidance on management of young people with cancer in specified regional principal treatment centres following age-appropriate protocols and treatment in specialist units [47]. This is resulting in a growing population of long term survivors who need long-term follow-up and catering for their needs to minimize morbidity, prevent secondary cancer and to normalize their

lives. Future work should analyse geographical patterning in cancer survival and other factors that may lead to delays in diagnosis [48].

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Conflict of Interest statement

The authors have no competing financial interests or any other conflicts of interest.

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The Figures' legends

Figure 1. Kaplan-Meier survival plot for all cancers aged 15 – 24 by time period of diagnosis (N = 2,987).

Figure 2. Kaplan-Meier survival plot for all cancers aged 15 – 24 by gender (N = 2,987).

Figure 3. Kaplan-Meier survival plot for all cancers aged 15 – 24 by age group (N = 2,987).

Supplementary Figure 1. Kaplan-Meier survival plot for leukaemia cases aged 15 – 24 by period of diagnosis (N = 344).

Supplementary Figure 2. Kaplan-Meier survival plot for lymphoma cases aged 15 – 24 years by period of diagnosis (N = 713).

Supplementary Figure 3. Kaplan-Meier survival plot for central nervous system tumours aged 15 – 24 years by period of diagnosis (N = 446).