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Title:

Survival patterns in teenagers and young adults with cancer in the United Kingdom: comparisons with younger and older age groups

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The corresponding author has ensured that all co-authors are in agreement with the submission, content and presentation of this paper.
Abstract

Aims: We aimed to describe and compare survival in teenagers and young adults (TYAs) with cancer to that of younger children and older adults, to identify sub-populations at greater or lesser risk of death. Methods: We compared survival in cancer patients diagnosed in the United Kingdom aged 13-24 years (TYAs) to those aged 0-12 (children) and 25-49 years (adults) using the National Cancer Data Repository. All cases had a first cancer diagnosis between 1st January 2001 and 31st December 2005 with censor date 31st December 2010 or death if earlier. Results: We found six distinct statistically significant survival patterns. In pattern 1, the younger the age-group the better the 1- and 5-year survival (acute lymphoid leukaemia, carcinoma of ovary and melanoma). In pattern 2, TYAs had a worse 5-year survival than both children and young adults (bone and soft tissues sarcomas). In pattern 3, TYAs had a worse 1-year survival but no difference at 5-years (carcinoma of cervix and female breast). In pattern 4, TYAs had better 1-year survival than adults, but no difference at 5 years (carcinoma of liver and intrahepatic bile ducts, germ cell tumours of extra-gonadal sites). In pattern 5, the younger the age-group the better the 5-year survival, but the difference developed after 1-year (acute myeloid leukaemia, carcinoma of colon and rectum). In pattern 6, there was no difference in 1- and 5-year survival between TYAs and adults (testicular germ cell tumours, ovarian germ cell tumours and carcinoma of thyroid). Conclusion: TYAs with specific cancer diagnoses can be grouped according to 1- and 5-year survival patterns compared to children and young adults. To further improve survival for TYAs, age-specific biology, pharmacology, proteomics, genomics, clinician and patient behaviour studies embedded within clinical trials are required.
**Key Words:**

Adolescent  
Young adult  
Teenage  
Neoplasms  
Survival analysis  
Cancer survival  
Teenager and young adult cancer  
Central nervous system tumours  
Haematological malignancies  
Bone tumours
Introduction

In people aged 13-24 years, cancer is the leading cause of non-accidental death in the UK[1]. While some cancer types (such as Hodgkin’s disease, germ cell tumours and melanoma) have excellent survival, others (such as sarcomas and central nervous system (CNS) tumours) have much poorer results[2-4]. Although cancer outcomes have improved, teenagers and young adults (TYAs) may not have seen the dramatic improvements seen in younger children and older adults[5].

Our aim was to estimate 5-year survival rates for TYAs aged 13 to 24 years with cancer in the UK and identify survival patterns, in comparison with younger children and older adults, to identify sub-populations at greater or lesser risk of death. This can direct hypotheses underpinning the outcomes observed. We also aimed to partition survival rates over follow-up time. In cancers where prognosis with prompt treatment at an early point in the disease history is good, comparatively lower 1-year survival may be due to advanced stage at diagnosis, deaths from peri-operative or treatment toxicity and (rarely in young people) co-morbidity[6]. Lower 5-year survival conditional upon surviving 1-year indicates clinical deterioration after initial successful therapy, and therefore differences in the longer-term effectiveness of patient management; differences due to variation in biology between age-groups or in treatment, pathways of care, clinician or patient behaviour[7, 8].
Materials and Methods

We analysed survival at one and five years from diagnosis for TYAs between the ages of 13 and 24 years by cancer diagnosis, and compared with survival of younger children (0-12 years) and older adults (25-49 years) for the seventeen most common cancer diagnostic groups affecting TYAs in the UK; acute lymphoid leukaemia, acute myeloid leukaemia, non-Hodgkin’s lymphoma, Hodgkin’s disease, CNS tumours, bone tumours, soft tissue sarcomas, testicular germ cell tumours, ovarian germ cell tumours, germ cell tumours of non-gonadal sites, melanoma, carcinoma of thyroid, carcinoma of colon and rectum, carcinoma of liver and of sites in gastro-intestinal (GI) tract, carcinoma of ovary, carcinoma of cervix, carcinoma of female breast. We examined the 5-year survival conditional upon surviving one year after diagnosis, i.e. removing deaths within the first year, maintaining consistency with earlier work looking at early and late survival[6, 8].

One- and five-year survival estimates were based on cancer registration data for all patients resident in the United Kingdom aged between 0 and 49 years, with a first malignant neoplasm diagnosis or a diagnosis of borderline or benign CNS tumour, between 1st January 2001 and 31st December 2005. The censoring date was 31st December 2010, or earlier death. The dataset includes all diagnosis information held by the National Cancer Data Repository (NCDR) excluding identifiable data. The NCDR is a compilation of all cancer registry data undertaken by National Cancer Intelligence Network (NCIN). It was obtained through North West Cancer Intelligence Service (NWCIS) which is the lead registry for cancer in TYAs in England. Diagnoses were grouped using ICD-0-2 topography[9] and morphology codes TYA classification scheme[7].

Death certificate-only registrations (1.9% across all ages), any case with a date of diagnosis equal to date of death and individuals with a previous cancer diagnosis prior to 2001 were excluded. A diagnostic group was excluded if the number of new cases with that diagnosis per year was fewer than 10 to avoid unstable results. Where the total number of cases in a single age-group was less than 5, no data are shown to preserve confidentiality. Ascertainment of those aged under 15 years diagnosed
with cancer in 2003-2004 is almost complete [10], while no formal evaluation of the completeness of registration of cancer in 15-24 year olds was conducted. At the level of main diagnostic categories (per the Birch et al classification[7]), 98% of cancer registrations are sufficiently detailed to be allocated to the main categories. In the UK cancer registries receive weekly copies of death certificates of all individuals who died in their region on whose death certificate cancer is mentioned. Registries also receive monthly copies of death certificates of any patient registered with cancer by that registry if the death certificate does not mention cancer or the patient died in another region.

The survival probabilities were estimated using the Kaplan–Meier method[11]. Expected survival was estimated using the Ederer II method[12], using Stata STRS[11] and UK life tables from Office for National Statistics for the years 2001 to 2010[13]. Survival was estimated as the ratio of the observed survival of the patients (where all deaths are considered events) to the expected survival[14]. Five year survival conditional upon surviving one year was taken as the ratio of the survival estimate at five years and the survival estimate at one year.

5-year relative survival was modelled using multiple regression based on linear models, using the Poisson assumption for observed deaths, adjusted for age. The excess hazard ratios of death derived from the models quantified the extent to which the risk of death in the older and younger age-groups differed from that in the 13 to 24 year age-group after considering the background risk of death in the general population[11]. Differences were considered statistically significant if P values were < 0.05 in a two-sided test.
Results

The incidence of cancer increased greatly with increasing age. In the 0-12 years age group between 2001 and 2005, there were 5,237 cancers identified, rising to 9,894 in the 13-24 age group. Despite the 25-49 years age band being only twice as wide, the older age group had a cancer incidence of 131,802 cases.

There are six survival patterns, five of which are represented in the fourteen Kaplan-Meier graphs shown in Figures 1 to 5. Pattern 6 is not represented graphically as there were no survival differences. Figure 6 illustrates three diagnoses with no pattern in common with other diagnoses. Table 1 shows the results of statistical analyses. Diagnostic groups in the 0-12 age group with insufficient numbers to present the data are testicular and ovarian gonadal germ cell and trophoblastic neoplasms, melanoma, carcinoma of thyroid, carcinoma of colon and rectum, carcinoma of liver and ill-defined sites in GI tract, carcinoma of ovary, carcinoma of cervix and carcinoma of breast.

Pattern 1 was seen in acute lymphoid leukaemia (ALL), carcinoma of ovary and melanoma (Figure 1). The younger the age-group, the better both the 1- and 5-year survival. In ALL, survival differed markedly by age (p <0.001 for older adults and young children compared to TYAs at both 1 and 5 years). The 5-year survival difference was also marked in carcinoma of the ovary between TYAs and adults.

Pattern 2 was seen in bone tumours and soft tissue sarcomas (Figure 2). These were the only diagnoses where the TYA age group had worse 5-year survival than both young children and adults. In bone sarcomas 5-year survival in young children and adults was 9 percentage points better than for TYAs. Comparing early and late deaths, the difference in outcome between TYAs and young children was present at both 1 and 5 years, whereas the difference between TYAs and adults was only present at 5 years. Comparing early and late deaths in soft tissue sarcomas, the difference in outcome
between TYAs and the two other age groups was seen predominantly in the 5-year conditional upon 1-year survival with a 10% absolute survival difference between TYAs and adults.

Pattern 3 was seen in carcinoma of cervix and of the female breast (Figure 3). These were the only diagnoses where TYAs had statistically significant poorer 1-year survival, but no difference at five years compared with adults.

Pattern 4 was seen in carcinomas of the liver and intrahepatic bile ducts and germ cell tumours of non-gonadal sites (Figure 4). These are the only diagnoses where TYAs had a markedly better 1-year survival than adults, but no difference was identified at 5-years. TYAs with carcinoma of liver is rare (57 in TYA group, 645 in adult group).

Pattern 5 was seen in acute myeloid leukaemia (AML) and carcinomas of colon or rectum (Figure 5). These are the only diagnoses where the younger the age group the better the 5-year survival, but 1-year survival difference was not statistically significant comparing all age groups. In AML the difference in 5-year survival was statistically significant. At 1-year, the difference was only significant between TYAs and adults.

Pattern 6 was seen in testicular germ cell tumours, ovarian germ cell tumours and carcinoma of the thyroid. These were the only diagnoses where there were no meaningful differences in survival between TYAs and other groups at either 1- or 5-years.

Figure 6 shows the diagnoses where the survival pattern did not conform to a 1- and 5-year survival pattern shared with other diagnoses. In Hodgkin’s disease 5-year survival was very high in all age groups. TYAs had better survival at both 1 and 5 years than adults, and there was no statistical difference in survival between TYAs and children. In non-Hodgkin’s lymphoma, the only observed statistical difference in survival was the better 5-year survival of children compared to both TYAs and
adults. This difference accumulated after one year. Neoplasms of the central nervous system was the only diagnostic group where TYAs had better 1- and 5-year survival than both children and adults.

Figure 7 compares the 5-year survival patterns by diagnosis. The steep gradient in carcinoma of the ovary and ALL make the marked difference in 5-year survival between age groups apparent. The differences in absolute survival among diagnoses clustered within one of the 6 described patterns is apparent.
**Discussion**

We identified differences in one and five year survival between the age groups examined and clustered diagnoses according to the statistical pattern of TYA survival compared to children and young adults. There were three diagnoses where TYA survival stands distinct from both comparator age groups; TYA 5-year survival was better in CNS tumours and poorer in both bone and soft tissue sarcomas. Table 2 summarises the 6 patterns observed and considers the implications.

Examining the 5-year conditional survival may indicate effects of differences in treatment selection and efficacy. Where the differences in survival were mainly due to events in the first year, this may be due to stage of disease at diagnosis, aggressive disease or mortality from initial treatment. These scenarios will be influenced by disease biology and the approaches to symptoms and management of both the patients and clinicians.

In the UK the age of 13-24 years is frequently used in clinical departments for the TYA age range[15], for the provision of specialist facilities and the reach of multidisciplinary teams. The same age range was used in a previous survival analysis[2]. We also restricted the upper limit of the TYA age range to 24 years to increase the likelihood of comparable treatment delivery within the group[16]. Using adults aged 25 to 49 years offers tumours with the most comparable biology to those of the TYA population[17, 18]. Using 49 years as the upper age limit for adults limits the influence of national screening and referral guidelines for persons aged over 50 years upon our comparisons. At the time of planning this study, national guidance stated that individuals with certain symptoms should be referred for investigation of suspected cancer if 50 years or over[19]. This was the case for breast cancer, ovarian cancer, upper GI cancers, and the lower age limit for breast cancer screening was 50 years.
In acute lymphoid leukaemia, survival became markedly and progressively poorer as age at diagnosis increased. Future work will examine whether trends in outcome continue based upon age as newer treatment protocols are implemented[20]. TYAs are known to have lower survival than children for osteosarcoma and Ewing sarcoma and there is some indication that older adults with these tumours have higher survival [21, 22]. The higher adult survival in bone sarcomas is likely to reflect the higher proportion of tumours with better prognosis, such as chondrosarcomas[23, 24]. The lower TYA survival in soft tissue sarcoma may be due to the less favourable case-mix including Ewing’s family of tumours of soft tissue and alveolar rhabdomyosarcoma [24]. In the United States, however, there was no evidence of lower survival of TYAs with soft-tissue sarcoma, but marked variation in survival by age for several histological sub-types[25].

Our findings in colorectal cancer suggest a difference may be due to the impact of clinical management, such as response to therapy. The modal age of onset of this disease is 80 years[26], and the proportion of patients with inherited genes that confer increased risk of cancer is likely to be higher in patients who are young at disease onset[27]. Patients who inherit a genetic predisposition to cancers may have different responses to treatment, which could explain some of the variation in survival[28]. Inherited genetic predispositions may play a part in understanding survival patterns in breast cancer[29]. In malignant melanoma, distinct biology in younger onset disease has recently been identified [30], such as potential of the presence of BRAF mutations to influence both outcome and therapy[31]. Both carcinomas of the cervix and of the female breast showed poorer 1-year survival in the TYA age group but equivalent 5-year survival compared to adults. This may imply more advanced disease at diagnosis, possibly secondary to the minimum age of cervical screening in the UK being twenty-five years.

We compared these results to United States Surveillance Epidemiology and End Results (SEER) data relating to diagnosis between 1993 and 1997[32] and the 2000-2008 data, noting that this uses 15-39 years to represent TYAs[33]. SEER data from 1993 to 1997 demonstrated poorer 5-year survival outcomes for US patients aged 15-24 years than either younger children or older adults when they
developed breast or colorectal carcinomas, soft tissue sarcoma, non-Hodgkin lymphoma or leukaemias. They also demonstrated poorer outcomes for 15-25 year-olds than younger children with Hodgkin lymphoma, cervical carcinoma, ovarian cancer, brain tumours, Ewing sarcoma of bone, acute lymphoblastic leukaemia and primary hepatic cancers. Disparity in survival seems more widespread in the US in 1993-7 than we have demonstrated. We acknowledge progress in diagnosis and treatment of cancer has been made in the intervening 10 to 15 years which impacts on survival of patients. The survival disparity is less apparent in the 2000-2008 SEER data where 15-39 year olds had poorer 5-year survival than adults only in female breast cancer, cervical and uterine cancer and poorer 5-year survival than children in ALL, AML, bone sarcoma and soft tissue sarcoma. Possible explanations for international differences include definition or requirements for inclusion within registry data[2]. In the UK benign and borderline CNS tumours are included when calculating survival for CNS tumours, while these are usually excluded from US analyses. The two populations have had different entitlements to high quality health-care due to status of health insurance[34] and entitlement to TYA-tailored specialist care as in the UK NHS[35].

Progress is being made in the UK in the provision of specialist environments and clinical teams for TYAs with cancer[35]. National guidance defines the infrastructure required for this, in regional principal treatment centres and specific ‘designated’ smaller treatment centres[36]. Referral pathways for young people with cancer are mandated by the National Health Service.

The main strength of this work is that the survival estimates are based on data from a long-standing cancer registration system with population based coverage[6]. The proportion of death certificate only registrations is low, but there are a number of potential biases that could result in underestimation or overestimation of survival rates. Survival would be overestimated if deaths for a sizeable proportion of registered patients were not added to the registry records, such as patients lost to follow up. The proportion of patients lost to follow-up in this study is unknown. The two ways, outlined in the methods, used to inform registries of the death of cancer patients should result in the vast majority of deaths being recorded, however empirical evidence in this age group is lacking.
Completeness of case ascertainment of the UK cancer registration using other data sources and in simulation models concluded that case ascertainment is 98-99% and it would have to be considerably lower to have a noticeable effect on survival estimates[37-39]. The recent setting up of a single cancer registry for England accompanied by the collection of better diagnostic, staging and treatment details should result in survival estimates of the highest quality but also in determining the relationship between low survival and patient management[40]. Some of the differences may be due to chance alone such as in carcinoma of the liver where the numbers are small and therefore estimates of survival may not be accurate, but also small numbers could result in insufficient power to demonstrate statistical significance when a true difference exists such as in ovarian germ cell tumours and germ cell tumours of non-gonadal sites. Diagnoses were grouped using the ICD-O-2 classification as this was used by registries to classify tumours diagnosed in 2001 to 2005[9], but this has since been superseded by ICD-O-3. Use of ICD-O-2 may have increased the chances of diagnostic misclassification. The period of study was limited to 5 years for comparison with other studies [6]. Stage at diagnosis varies with age[41], but stage data was not available for inclusion in this analysis. It was not feasible to conduct analysis by histological subgroups due to small patient numbers. Borderline ovarian tumours are more common in TYAs, which may limit our analysis of ovarian carcinoma[42]. Similarly, the grades of neoplasms of the central nervous system vary with age[43]. A strength of this study is the addressing of differentials for the survival patterns and cancer diagnoses by age, which raises awareness regarding access to health services, compliance with treatment or variable biological response to treatment necessitating revision of treatment protocols by age.

In conclusion, TYA cancer care in the UK has been consolidating its progress in supporting age-appropriate environments and specialist teams for care. We have demonstrated 1- and 5-year survival patterns in TYAs by diagnosis compared to children and young adults. To further improve survival for TYAs, age-specific biology, pharmacology, proteomic, and genomic studies embedded within clinical trials are required. There is also a need for future detailed studies including histological subtype and cancer stage along with clinical treatment data, and over wider geographical populations.
Health services research should feature as a significant part in investigating and improving known differences in the TYA population such as delays to diagnosis[44] and participation in clinical trials to explain our findings, and improve survival.

**Conflict of Interest Statement**

Dan Stark declared relevant income from the Teenage Cancer Trust.

No other conflicts of interest declared.
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