

ENCCA WP17-WP7 consensus paper on teenagers and young adults (TYA) with bone sarcomas

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Teenagers and young adults (TYA) cancer contributes substantially to morbidity and mortality in a population with much to offer society. TYA place distinct challenges upon cancer care services, many reporting feeling marginalized and their needs not being met in adult or paediatric cancer services. Bone tumours such as osteosarcoma and Ewing sarcoma, because of their age at presentation and the complexity of their care, are where challenges in managing (TYA) with cancer have often been most readily apparent. Bone sarcomas may be managed by paediatric or medical oncologists, and require fastidious attention to protocol. A lack of recent improvement in survival in TYA with bone tumours may be linked to a lack of specialist care, poor concordance with therapy in some situations and TYA-specific pharmacology. Participation in clinical trials, particularly of young adults, is low, hindering progress. All these requirements may be best met by a concerted effort to create collaborative care between adult and paediatric experts in bone sarcoma, working together to meet TYA patients' needs.

Key words: osteosarcoma, bone tumours, Ewing sarcoma, teenage and young adults (TYA), adolescents and young adults (AYA)

introduction

Teenagers and young adults (TYA) have a significant burden of cancer, contributing substantially to morbidity and mortality in a population with much to offer society in the present time and in the future. They develop a range of cancers distinct from other age groups, and place particular challenges upon existing cancer care services to meet their health care psychological and social needs while delivering effective and safe treatment [1]. Because of their age at presentation and the complexity of their care, bone sarcomas are a field of cancer care where the challenges in managing TYA with cancer have often been most readily apparent [2, 3]. Groups collaborating in European and global bone sarcoma trials have sought solutions for some of the challenges posed to successful recruitment and the day-to-day management of the necessary complex multinational trial infrastructure, stimulated by a lack

of evident improvement in survival in recent years [4]. The management of TYA with bone sarcomas remains an area that may be doubly challenging, and therefore collaboration may be particularly productive, to improve the outcomes for this patient group, all patients with bone sarcoma and TYA with other cancers.

The EUROPEAN NETWORK for CANCER research in CHILDREN and ADOLESCENTS (ENCCA) aims to establish a durable, European Virtual Institute for clinical and translational research in childhood and adolescent cancers that will define and implement an integrated research strategy and facilitate the necessary investigator-driven clinical trials to introduce the new generation of biologically targeted drugs into standard of care for children and adolescents with cancer. Two of the work packages in ENCCA—work package 7 (WP 7: integrating clinical trials and tumour biology research in bone sarcoma) and work package 17 (WP 17: teenage and young adults) are collaborating in the field of TYA with bone sarcomas, aiming to develop more efficacious and less toxic therapies that will maximize the quality of life of the increasing number of young survivors of cancer in Europe and allow TYA to assume their proper place in society.

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cancer in TYA and why they are different

Cancer is a substantial problem in young people, occurring 2.7 times more commonly between the ages of 15 and 30 years than during the first 15 years of life [5]. In the age range 15–24, cancer causes 11% of deaths [6]. Among 20- to 39-year-old people, cancer causes more deaths than any other disease except depression [7]. Morbidity from TYA cancer is substantial, with 20 000 people aged 15–24 in the EU diagnosed with cancer each year; one in every 200 TYA [8, 9]. Bone tumours specifically peak in incidence in TYA [10, 11]. In broad terms while some cancer types (such as Hodgkin's lymphoma and melanoma) see excellent survival, others (such as sarcomas of soft tissue and bone) see poorer results [6]. For many cancers (and particularly bone sarcomas), young adult patients have been reported to have less improvement in survival over time than younger or older patients; this difference being most pronounced in those aged 20–29 years [12].

The special challenges of providing optimal treatment of this TYA group is increasingly characterized internationally [3, 13, 14]. In simple terms, TYA are the older patients historically managed in paediatric services and the younger patients historically managed in adult services. The challenge is to avoid losing optimal care down a 'gap' [15]. TYA, at the interface between paediatric and adult oncology, may appear to develop many cancers in categories typical of the paediatric age range, as well as early-onset carcinomas and a range of cancers most prevalent specifically in TYA [16, 17]. However, even if TYA cancer appears to be the same clinically as a child's or adult's tumour, translational and clinical research should not assume that the biology is the same, as the differences are sometimes quite marked [18, 19]. Sadly, there is inconsistent clinical use of molecular diagnostics in TYA that may be central to understanding this [20].

When describing the challenges of treating TYA with cancer, different health systems use different definitions because their existing systems of care differ and legal jurisdictions vary: some systems use age-based criteria, others use definitions of competency [21]. Within specific health care systems, in the United States, the AYA group runs from 16 to 39 years, and in the UK, the TYA group runs from 13 to 24. Some countries have a policy of integrated multi-professional clinical teams discussing the management of TYA across traditional boundaries of paediatric and adult practice [22]. Meanwhile, others, including Germany, have no formal interaction, relying on local relationships to establish (or not) common approaches, with a boundary drawn at a clear age such as 18 years with no logic in cancer epidemiology or patient needs. The ENCCA TYA group is using sequential structured surveys and a Delphi technique to understand these differences and map an evolution in them over time (for those interested to contribute, contact d.p.stark@leedsth.nhs.uk).

TYA have a distinct biology. Their physiology (e.g. hormonal), pharmacology (e.g. drug clearance, protein binding, hepatic and renal function) and behaviour (in relation to alcohol, tobacco or street drug experimentation) differ from younger and older people. There are gender differences specifically within the TYA age range: females will reach earlier puberty than males and therefore change fat, muscle, height and weight, but as yet different treatment protocols recognizing this

are not being studied in TYA [18]. TYA have different renal, hepatic and haematopoietic capacities from other groups, such that protocols and dose guidelines developed in other groups may not provide maximal tolerated treatment and so may not optimize cure [19].

Much remains to be learned about TYA cancer. It is notable that TYA are often reported to have lower recruitment to clinical trials than younger children, and this seems particularly evident for young adult patients who are no longer cared for within the study-addicted paediatric oncology environment [18, 23–26]. The lack of trial participation has been linked to a gap of prognostic improvements for TYA with cancer when compared with younger children and older adults [12]. Differences in trial availability and recruitment result in heterogeneity in the selection of treatment, hampering our understanding of (and improvements in) the clinical outcome [20, 25, 26]. Many feel this contributes to the absence of dramatic improvements for TYA that have been seen in younger children and older adults [12, 26].

Early detection of cancer can be more challenging in TYA than in other age groups: there is a general lack of awareness of cancer risk during early adulthood, not only in young adults, but also in care providers and the public [7]. TYA have the lowest rate of primary care use of any age group [27]. In the United States, TYA with cancer may have a delay in diagnosis because of inadequate health insurance and consequently present with a more advanced stage of disease, correlated with worse prognosis and outcome [28].

Cancer treatment in TYA may present particular challenges in supportive care. Serious illness has a sudden and unique effect on TYA, disrupting not only physical and psychological health, but also social and educational well-being, at a changing and complex time where successful development is critical to future success. TYA have diverse levels of maturity, different temperaments and different needs and these needs are (at best) inconsistently met by either paediatric or adult care individually, not the focus for either, so marginal in both [29]. Factors usual and helpful in their life outside the hospital may be missing; typically dedicated TYA services consider internet access and perhaps a games table, but also places where they can take some time undisturbed, and an environment where they can interact with other TYA [30, 31]. TYA may also have poorer concordance with state-of-the-art protocols for treatment than other groups, which may account for some outcomes, but this seems to be less the case the more the environment and professionals are designed specifically for their needs [32, 33]. However, there remain a few well-developed TYA-specific cancer services. Services may be 'untutored in arranging ancillary medical, psychological and educational supports that are so important to people who are facing taxing treatment at a vulnerable time' [3]. There can be poor recognition of their autonomy, their need for support, to continue to meet rapidly changing life goals during treatment, their need for peer-group support, for staff with experience of young people. TYA themselves describe unsatisfactory experiences of care but can be effective advocates for improvements in their care [29, 34–36].

Prospective research is ongoing in the UK to identify how such TYA specialist care may influence patient-reported and bio-medical outcomes [37]. Society would be substantially

advantaged by more successful treatment of TYA with cancer, as they can then make their contribution in employment and wider society over a long period.

The development of specific age-based services for TYA is ongoing in some parts of the world, albeit at different speeds (Table 1). Historically, paediatric care ended at different ages in different countries, and so the challenges for managing TYA more apparent in different places at different times. The necessity to develop a third specialization in addition to traditional paediatric and medical (adult) oncology may be experienced as less pressing in European countries where paediatricians often care for older patients. However, there remains an interface, and the model of care and interface between adult and paediatric cancer care can be debated. If a division is proposed, based on expertise, then it would follow logically that a clear-cut paediatric cancer, such as osteosarcoma, might be proposed to best treated by a paediatric oncologist (even if the patient is aged 75) and adult cancers (such as melanoma) can be best treated by an adult oncologist (even if the patient is aged 3), but this is surely a recipe for disaster; not likely to be acceptable to patients and likely to exacerbate professional conflict, due to a lack of appropriate other general skills and lack of consensus as to what constitutes a ‘clear-cut’ case. In marked contrast, comprehensive services that exist have found by experience that they prefer to embrace collaborative management for all TYA cancers. Many now believe TYA with cancer require a concerted effort to create

collaborative care involving both adult and paediatric cancer professionals, acknowledging the uncertainties and working together across any care ‘gap’, each contributing their specific expertise. The need for such collaboration is broad and particularly apparent in the management of bone sarcomas.

epidemiology and biology of bone sarcomas in relation to TYA

Ewing Sarcoma and osteosarcoma both have their peak incidence in the TYA age range. Consequently, bone sarcomas make up 6% of the cancers diagnosed in TYA [38]. Under the age of 20 years, data on 5572 children and adolescents diagnosed with malignant bone tumours during 1978 and 1997 in Europe were extracted from the Automated Childhood Cancer Information System (ACCIS) database [39]. The age-standardized incidence is similar for boys and girls aged 0–14 years, but, among those aged 15–19 years, males had a higher incidence. Osteosarcoma accounted for 51% of bone sarcoma registrations among children and 55% among adolescents; Ewing sarcoma for 41% of registrations among children and 28% among adolescents.

International guidelines state that all patients with a suspected primary malignant bone tumour should be referred to a bone sarcoma reference centre or an institution belonging to a

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Table 1. Selected National Professional and Charitable organizations focusing on TYA cancer

Organization	Geographical region	Role	Website
Teenage Cancer Trust	UK	Vision of a future where young people’s lives do not stop because they have cancer. We make sure they are treated as young people first, cancer patients second and everything we do aims to improve their quality of life and chances of survival.	http://www.teenagecancertrust.org/
Canteen	Australia	Vision is to bring together all young people living with cancer ... to support, develop and empower young people living with cancer.	http://www.canteen.org.au/
Teen Cancer America	USA	A charity devoted to improving the lives of teenagers and young adults with cancer.	http://www.teencanceramerica.org/
ENCCA	European Union	ENCCA will create a sustainable ‘European Virtual Institute’ for clinical and translational research in childhood and adolescent cancers. ENCCA will integrate all relevant stakeholders, their expertise and viewpoints to ensure that the project is all-encompassing while remaining patient-centred. Works with other developing national groups in Spain, Italy, France and others.	http://www.encca.eu/Pages/home.aspx
Adolescent and Young Adult (AYA) Cancer Task Force	Canada	Pioneering work to investigate and increase awareness of treatment and survivorship issues.	http://www.partnershipagainstcancer.ca/2011/06/23/adolescent-and-young-adult-cancer-patients/
German Society for Paediatric Haematology and Oncology (GPOH)	German	Professional development in TYA cancer care, within the German Society for Paediatric Haematology and Oncology (GPOH).	http://www.kinderkrebsinfo.de/patienten/index_ger.html
Go AJA	France	Improve quality of treatment for TYA with cancer.	http://www.go-aja.fr

specialized bone sarcoma network before biopsy. At the centre, the case should be discussed at a multidisciplinary team meeting that ideally includes the radiologist who has interpreted the imaging, the pathologist who has reviewed the biopsy material, and the surgeon and oncologist undertaking treatment. Therapy should be offered within the framework of prospective (often collaborative, international) clinical studies, or—if no appropriate trial is available or if patients make an informed choice of non-trial treatment—guided by established treatment protocols [40].

Bone sarcoma outcomes are reported across health care systems and over time to be poorer in TYA than in younger children [19, 41]. One explanation may be bio-medical; a period of great physical change occurs in TYA and pharmacological differences, especially for the clearance, are reported, for example for methotrexate, a drug often used in the osteosarcoma treatment [18]. Gender-related differences in incidence and outcome have been observed particularly for both Ewing sarcoma and osteosarcoma, with relative under-dosing of males based on current dosing algorithms [19, 42]. Gender differences may also relate to disease presentation. In one analysis, male TYA with bone sarcomas tended to present with larger primary tumours compared with females [42].

Whatever the explanation, progress is difficult with low levels of research. In Germany, osteosarcoma represents 2.3% of cancers in the age group under 15 years (410 of 17 876 patients with cancer), 98.3% in this age group with osteosarcoma are registered within the national disease-specific study group. Ewing sarcoma represents 2.1% of cancers in the age group <15 years (361 of 17 876 patients with cancer) and 99.2% in these age group with Ewing sarcoma are registered within the national disease-specific study group [23]. For young adults with bone sarcoma, participation into clinical trials is unfortunately nearer 20% [24].

Ewing sarcoma

Expected 5- to 10-year survival probabilities for Ewing sarcoma are in the range of 55%–70% and above [23, 43]. One quarter of Ewing sarcoma patients are 15–20 years of age; there is an impact of age and gender, but TYA outcome appears worse than in younger children [10, 42]. Compared with younger Ewing sarcoma patients, TYA (>17 years) presented with larger tumours (≥ 13 cm), were more likely to be male and were more likely to have pelvic or axial tumour. Young adult age remained an independent poor prognostic variable even after controlling for these and other variables [44]. Other studies have also analysed potential correlations between Ewing sarcoma patients' ages and prognosis, but results have been inconsistent, and it remains unproven whether age in the TYA range by itself truly confers inferior survival [10, 42, 45, 46].

An analysis carried out by the (E)CESS group suggested that TYA patients with Ewing sarcoma cared for within their multi-institutional studies achieved better outcomes if treated at paediatric rather than other institutions and at institutions treating larger rather than smaller patient numbers [45], but neither finding was confirmed when investigating the more recent EURO-EWING dataset [10, 42, 45].

Adults are incorrectly perceived by some to tolerate treatment less well than children. International collaborative Ewing sarcoma

protocols are open for children and adolescents and it has been observed that some toxicities (neutropenia, thrombocytopenia and stomatitis) may even decrease with age [47, 48]. It remains to be determined whether less toxicity represents less treatment administered to older patients or whether other biologic factors can be held responsible.

osteosarcoma

Expected 5- to 10-year survival probabilities for osteosarcoma are 43%–70% and above [23, 49, 43]. The highest incidence of osteosarcoma is during the pubertal growth spurt, so females reach their peak incidence younger [11].

Lag time between the first signs or symptom and diagnosis may be particularly long in osteosarcoma and may be influenced by the type of health insurance [28]. Longer lag times seem to correlate with a larger disease burden at diagnosis [28, 50, 51]. While often assumed to be the case, there is no clear-cut evidence that TYA will experience longer diagnostic delays than younger or older patients or whether longer lag times are associated with TYA developing more (axial) tumours [52].

Age is, however, a strong predictor of trial participation. For instance even though the EURAMOS-1 trial was open for patients aged 0–40 years [53], the experience was that young adults were much less likely than children to be included into this trial, and then often by institutions primarily catering to a paediatric constituency [24]. Continuing efforts to promote collaborative working and study recruitment with teams managing young adults are clearly warranted. Given the experience obtained over the past decades; however, one should not be immediately optimistic that this will result in an overwhelming success unless such efforts are accompanied by other, major alterations of the focus on TYA specialist care, in particular in collaboration.

Age (as well as gender) appears related to treatment toxicities and prognosis. A recent very large meta-analysis of raw data of 4403 patients from five international co-operative groups included prospective osteosarcoma studies of adjuvant/neo-adjuvant chemotherapy conducted between 1979 and 2005 [49]. Multivariate landmark analysis following surgery indicated that a higher rate of chemotherapy-induced tumour necrosis was associated with longer survival, as was the incidence of grade 3 or 4 mucositis. Treatment toxicity and prognosis varied by age and gender: females had more thrombocytopenia than males. After accounting for variables such as tumour site and histology, females also experienced higher 10-year overall survival rates than males. Ten-year overall survival was 66% for children and 62% for adolescents and adults. Children reported higher rates of neutropenia and thrombocytopenia than adolescents and adults. On the other hand, children also enjoyed higher tumour necrosis rates and survival expectancies. Male adolescents and older adults experienced the lowest rates of treatment-related deaths and the poorest tumour necrosis across all groups. These results suggest differences in the way chemotherapy is handled by, or delivered to, children compared with TYA and older adults. Research to examine this is required, either to improve supportive care for TYA (enabling optimal treatment) or to understand differences in the tolerance of treatment. To achieve this, more TYA need to be entered into prospective trials.

consensus statements

- (i) Bone sarcomas and their treatment can typify key issues in TYA oncology. Ewing Sarcoma and osteosarcoma have a peak in incidence in the TYA age range. Their treatment is frequently long, multi-professional and complex, and optimal care requires fastidious attention to state-of-the-art protocols. This is doubly challenging, disrupting not only physical and psychological health, but also social and educational well-being, in services that patients report often do not meet their broader needs.
- (ii) According to the European Sarcoma Network Working Group (ESMO) Guidelines, all patients with a suspected primary malignant bone tumour should be referred to a bone sarcoma reference centre or an institution belonging to a specialized bone sarcoma network before biopsy [40]; for biopsy to be carried out at the reference centre with the surgeon who is to carry out the definitive tumour resection.
- (iii) Systematic collection and subsequent biological study of patient material is pre-requisite for effective research. Standard protocols to ensure proper legal accrual of this material should be integrated into clinical trials and treatment protocols.
- (iv) Some outcomes for TYA with bone sarcomas appear different comparing older adults and young children. Survival rates are generally higher for children than for TYA. Treating to maximum toxicity appears important; patients with higher toxicity from chemotherapy seem to have better cancer necrosis and better survival. TYA appear to have lower levels of each. We need to characterize these differences in more detail, and determine what factors may be contributing to these differences, such as (but not limited to) age, tumour biology, toxicity, gender, health care systems, presentation, lifestyle and clinical management. To do that, TYA need to be recruited to trials with integrated biological analyses.
- (v) Most patients with bone sarcomas >18 years included into multicentre trials are registered by institutions also caring for children and adolescents. Efforts to improve this for all treating TYA seem to be variable in their effectiveness, working better in Ewing sarcoma than in osteosarcoma.
- (vi) There is a low degree of specialist centralization and a longer lag time in diagnosis reported for TYA bone sarcoma patients—especially for young adults. Improvement in health service and clinical outcomes from bone sarcoma management can only be expected if the management is carried out by a specialist sarcoma centre with a large number of patients and specific infrastructure.
- (vii) The incidence and survival of bone sarcomas in TYA is age- and gender-dependent, and this may influence the lack of survival benefit in TYA. Therefore, further studies might examine age and gender-adapted dosing of chemotherapy
- (viii) There is a variable amount of TYA specialist care available; many TYA are currently managed by either paediatric or adult oncologists without a strategy to optimize this in many countries. Improving this requires collaboration between adult and paediatric specialists, to meet the breadth of patients' needs.
- (ix) This collaboration should aim to improve recruitment of TYA with bone sarcomas to clinical trials, with integrated biological analyses, if we are to develop treatments with improved efficacy and toxicity, based on research into specific age differences.
- (x) Paediatric and adult cancer services and different medical and non-medical disciplines need to collaborate across traditional age-based boundaries to meet the needs of TYA. Leaders in TYA and bone sarcoma oncology may lead this collaboration.

conclusion

Bone tumours such as osteosarcoma and Ewing sarcoma have often been the area where TYA issues are most readily apparent; they may be managed by paediatric or adult oncologists according to local factors rather than patient-centred or logical design. A lack of recent improvement in survival in TYA with bone tumours may be linked to a lack of recruitment into trials for some groups, a lack of specialist care, poor concordance with therapy where specialist care is not in place and/or TYA-specific pharmacology. Because, unlike paediatric oncologists, adult oncologists may not be 'study addicted', and perhaps because recruiting to trials in TYA can be more difficult without TYA-specific teams, participation in clinical trials is low in young adults. All these problems may be best met by a concerted effort to create collaborative care between adult and paediatric experts in bone sarcoma, working together to meet TYA patients' needs.

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disclosure

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