
Article:
Hughes, N and Stark, D orcid.org/0000-0002-6172-733X (2018) The management of adolescents and young adults with cancer. Cancer Treatment Reviews, 67. pp. 45-53. ISSN 0305-7372

https://doi.org/10.1016/j.ctrv.2018.05.001

Title: A review article: The management of adolescents and young adults with cancer

Authors: Nicola Hughes[1] and Dan Stark[2]

1. Leeds Institute of Cardiovascular and Molecular Medicine, University of Leeds, UK.

2. Leeds Institute of Cancer and Pathology, St James's Institute of Oncology, Beckett Street, Leeds, UK

Keywords: Adolescent, Young Adult, Cancer, Epidemiology, Survival, Psychosocial, Clinical Trials, Biology, Training, Palliative Care, Late Effects, Survivorship.

Abstract

Adolescents and Young Adults (AYA) with cancer are young people developing serious illness when at the interface between the responsibilities of paediatric and adult cancer services. Personally, they are in a period of transition both biologically and in major social roles[1]. For these and other reasons they present a unique set of clinical challenges in their management. Over the last 20 years the need for specific services to address their needs has been identified and this has become a growing field of research. Despite this survival rates still lag behind those of children and older adults with cancer[2].

Why do AYA patients have worse outcomes? The observation is that the reason is multifactorial with path to diagnosis, unique cancer biology, uncertainty of treatment protocol, compliance issues and poor recruitment to clinical trials all playing a part. In this review we will discuss the unique challenges faced by healthcare professionals when managing AYA patients who are commonly and accurately described as being in an 'interface' position.

The Adolescent and Young Adult (AYA) population

The age classification of adolescent and young adults (AYAs) encompasses different age groups depending on purpose. Adolescence is defined to range from 10 to 19 years[3]. For the purpose of active treatment this increases to the mid 20s, up to 30 years for epidemiological studies and 40 years for clinical follow up[4]. In the UK we focus on teenagers (13-18 years) and young adults (19- 24 years) forming the Teenage and Young Adult (TYA) patient group. Although some may find this lack of consensus unnerving, maintaining flexibility enables the needs of this patient population to be met more freely. Thus reducing the risk that such patients fall into gaps between services, an outcome which AYA services are trying to avoid[5]. In this review the term AYA will encompass the age range 15-39 years as proposed by the National Cancer Institute and supported by ENCCA[6].

Epidemiology

Cancer is the leading cause of disease-related death in people aged 15-24 years old and is exceeded only by cardiovascular disease in 25-39 year olds. Throughout Europe it is the third most significant cause of

mortality in young people, behind road traffic injuries and suicide[3]. Globally the annual incidence of cancer in 15-39 year olds is estimated at one million, with approximately 66,000 cases in Europe per year[7]. Across North America and Western Europe the overall incidence of AYA cancers is slowing increasing. The rates differ between cancer types and may be partially attributed to external factors, for example the increase in Thyroid cancer in North America may be due to evolving diagnostics. Projections in the UK are that rates will continue to rise particularly within germ cell tumours in men and carcinomas in females [8].

The most commonly occurring cancers types in AYAs are; haematological malignancies (mostly Hodgkins's and non-Hodgkin's lymphoma), carcinomas (notably breast, thyroid, melanoma and gynaecological) and germ cell tumours[7]. The distribution of cancer types across the AYA age group is demonstrated in Figure 1.

The aetiology of AYA cancer remains relatively unknown and understudied. Germline mutations account for less than 5% of cases in the AYA age group. It has been considered that they are caused by a combination of congenital and prenatal factors, seen in childhood cancers and environmental cancers seen in adult cancers, although with different latencies[9]. Other causative factors may be attributable to puberty and the stage of life. For example the incidence of osteosarcoma rises after puberty in long bone sites that undergo rapid growth at this time, the earlier onset of pubertal growth in females is also apparent [10].

Traditionally survival rates for AYA's have been poor and improvements have lagged behind that of paediatric oncology patients. Analysing US SEER data Bleyer et al. showed that improvement in survival rates for patients aged 15-45years old was a fraction of that in children in older adults. For those aged 25-35 years there was no evidence of any improvement (figure 2).[11].

An increased interest in the field of AYA oncology and the identification of the need to recognise this group of patients as a distinct cohort with their own unique needs has improved outcomes. In their European study looking at survival of teenagers and young adult cancers Trama et al. showed 5 year relative survival for all cancers combined to have improved from 79% in 1999-2001 to 82% in 2005-2007[12]. EUROCARE-5, a population-based cancer registry study, looked at the 5-year relative survival of AYA patients in comparison to childhood and adult cancers. This showed that the overall five year survival for all cancers in AYA patients is now greater than 80% in high-income countries. Survival rates however were still lower than in children for eight cancers: ALL, AML, HL, non-HL, astrocytomas, Ewing sarcoma and rhabdomyosarcoma[12]. AYAs survival rates for fibrosarcomas, soft tissue sarcoma and acute myeloid leukaemia remained stable.

Cancer Biology

AYA patients and their cancers both display specific biological characteristics[13] which influence their response to treatment and thus prognosis. This can be a positive factor, for example melanomas with BRAF mutations are more prevalent in the AYA population and thus are more likely to respond to a BRAF inhibitor[14]. Less favourably, triple negative breast cancer is more prevalent in patients under 40 years and is associated with increased mortality partly due to fewer treatment options[15]. In comparison to children, AYA patients with Acute Lymphoblastic Leukaemia (ALL) have a higher proportion of

unfavourable genetic abnormalities such as Ph-1 and a lower proportion of those which are treatment responsive. The TEL-AML1 translocation in ALL has a favourable response to treatment and is found in only 10% AYA cases as opposed to 50% of childhood cases[16]. AYA patients with rhabdomyosarcoma are more likely to have the more aggressive alveolar subtype[17]. As the molecular characterisation of cancers advances the hope is that patients will be able to be treated with more individualized protocols which may improve outcomes in AYA patients and develop AYA-specific clinical trials. Studies in synovial sarcoma[18] and rhabdomyosarcoma [19] have demonstrated the potential to use identifiable genetic differences within cancer subtypes as decision aids in clinical management to identify those in need of high risk treatment.

Model of care

AYA patients were historically treated in either a paediatric setting or an adult oncology setting. The former takes a family centred approach and threatens the AYA's autonomy, impacting upon emotional wellbeing. The adult setting focuses on the disease and not the complex psychosocial needs of the AYA, impacting upon concordance with treatment. AYAs are at an age where they are developing very rapidly in areas such as independence from the family unit. Each individual patient will vary in how far along their transition to independence they are at any one time and this will change during their cancer management, often quite dramatically. Thus presenting their own evolving and fluctuating challenges in terms of information, communication and decision-making preferences. A model of care is required that keeps the best of the two traditional approaches for AYA and omits the rest [20]. Achieving this however is not always easy[21].

The care environment needs to be tailored specifically to the needs of AYA patients. Inpatient wards with colourful décor and facilities such as relaxation areas, games consoles and music facilities provide patients with an environment they can be happy to attend, something approaching normality, a feeling that their needs have been identified by the hospital, and a forum in which they can build peer relationships with fellow patients. They can also enable services to provide specifically trained therapists and youth workers in an informal manner, which has been found to be beneficial to AYAs[22].

The rarity of AYA cancers also means that in order to receive the best treatment they should be cared for in specialist centralised centres by health care professionals with expertise in AYA cancers who have regular exposure to managing their cancers[23][24]. The care needs to be provided by an extensive multidisciplinary team that not only encompasses the traditional medical specialists but other healthcare professionals such as clinical psychologists, teachers, social workers and fertility experts. Thus addressing all needs of the AYA patients and not just their cancer. Care in specialist centres can also prevent feelings of isolation from other young people[25]. Table 1 describes the different models of care used across Europe as outlined by Stark *et al*[5].

Within England centralisation began after the National Institute of Clinical Excellence published guidelines on 'Improving Outcomes Guidance for cancer in children and young people'. These were then supplemented in 2014 with seven statements prioritising areas for service improvement. Under this guidance patients aged 18 years or below at time of diagnosis must start their treatment at a principal centre after that it is possible for them to attend a more local designated hospital if they wish. Patients aged 19-24 years have the option of attending a principal centre or designated centre but this decision needs to be an informed choice.

Of course, there are negative aspects to centralised care. Notably the geographical distance that some patients and their families may need to travel in order to access these services, meaning disruption to friendships, education and careers that are so important at this age. AYAs are prone to challenge the views of their elders and for this reason it is beneficial to incorporate their views into developing services which is being done in a number of settings internationally[26]. The BRIGHTLIGHT study is completing research involving previous and current patients to address the question "do specialist services for the teenage and young adults with cancer add value?[27]" Other novel approaches to encouraging AYA patients to express their views include through music[28].

Equally as important as where AYAs receive their care is who is providing it. The complex needs of AYA patients requires health care professionals to be educated and skilled not only in the unique biology and treatment requirements of their cancers, but also their psychosocial issues and communication challenges [29] . They need to be able to effectively communicate with AYAs, their families and peers and embrace the challenges that they bring[22]. They need to expect and be prepared in advance for the positive and negative approaches to information and care routinely observed in young people, such as challenging authority and fluctuating tensions within families.

An international multicentre study identified a list of competencies required by healthcare professionals working in AYA services. Competences such as identifying the impact of disease on a young people's life, ability to discuss sensitive subjects and ability to use humour appropriately ranked highly. These findings can be used to influence educational curriculum, professional development and inform workforce planning[30]. This is important as the skills required are not adequately covered in the traditional adult or paediatric training programmes[31]. The consensus of AYA cancer and Medical Education experts at an international summit meeting hosted by ENCCA and The Teenage Cancer Trust in 2014 included:

- That TYA specific education is needed and should be accredited by Universities, in collaboration with professional societies.
- There should be generic "working with AYA" training programs for all health care professionals who work with young people with serious illness.
- Detailed AYA training should become, in time, compulsory for all doctors leading in AYA cancer care, who should then hold a validated qualification in AYA oncology.

In the UK a collaboration between the Royal Colleges of Paediatrics and Child Health, Nursing, General Practice, and Obstetricians and Gynaecologists has produced an online e-learning module aimed at equipping health professionals with the communication skills required to work with AYAs. Training curricula for AYA are being established in the UK, US, Canada, Australasia and the EU. In Europe the European Network for Teenagers and Young Adults with Cancer (ENTYAC) aims to develop specific practice guidance for AYAs[5] and the European professional societies for medical oncology (ESMO) and Paediatric Oncology (SIOPE) are actively collaborating on professional education in AYA cancer care[32]. What is interesting is that although the curricula require a similar knowledge base they differ in the additional skills and attributes needed, which may reflect the different care models used in these countries[29][33][34]. In an age where we rely heavily on the internet, directing patients and family members to reliable internet resources may be a useful and underused communication adjunct[35].

Treatment – age appropriate protocols

AYA patients present treatment related challenges not only due to the distinct biology of their cancers as discussed earlier but also the physiological state of their bodies during this stage of life. During the normal process of puberty a number of physiological and physical changes occur in the body which can influence the absorption, distribution, metabolism and elimination (ADME) of drugs throughout the body. These include hormonal changes, changes in body fat composition and organogenesis of the liver and kidneys[36]. The age of onset of these changes varies in each individual patient and is different in males and females[36].

Uncertainty exists regarding what dose intensity of treatment AYA patients should receive. In the mid-2000s a number of international groups compared outcomes of AYA patients with ALL treated with adult versus paediatric protocols[37][38][39][40][41][42]. Findings demonstrated superior complete response rates, event-free and overall survival for patients treated on paediatric protocols. Recent data in Canada introduced some doubt when implementing a change of protocols for AYA[43].

Work in osteosarcoma has found that within the same chemotherapy protocols AYA patients are receiving lower doses of chemotherapy, fewer toxicities and worse outcomes. This study suggests that age and sex dependent pharmacological differences play a part[44]. There was previously a misconception that AYA patients were unable to tolerate the toxicity of paediatric chemotherapy protocols. Recent studies however have shown this is not the case; using the EURO-EWING 99 protocol, adults experienced less toxicity than children[45]. Older patients treated for rhabdomyosarcoma experienced less toxicity than younger patients[46]. The degree of myelosuppression seen in patients after chemotherapy has been shown to correlate with outcomes[47][48]. It may therefore be the case that poorer outcomes in AYA patients is related to lower systemic exposure to chemotherapy as reflected in the lower observed toxicity[46].

In comparison to older adult patients AYA patients are often able to tolerate more intense chemotherapy regimes, due to them having fewer comorbidities. Dose dense and dose intense regimes have improved outcomes[49] and every attempt should be made to maintain dose intensity. Barriers to this include the need to avoid irreversible end organ damage which will negatively impact long term quality of life. Compliance with therapy (see later) is also an issue for many. Monitoring for cumulative side effects is an essential component of care during active treatment. The place of care may also influence this as non-specialist centres may be inexperienced and unwilling to give the high dose intense treatments required.

As with cancer patients of all ages supportive management of treatment associated toxicities should be an integral part of cancer care to enable patients to complete treatment [50]. The ADME of supportive ancillary medications such as antiemetic and analgesic also needs consideration. Physiological differences may also make AYAs more susceptible to some side effects. For example poorer emesis controlled coupled with more aggressive regimes may result in increased susceptibility to anticipatory nausea and vomiting[51]. The use of steroids may be limited by acne, which some patients may find an unacceptable side effect. Experimental use of alcohol, illicit drugs and tobacco along with compliance issues to treatment can also influence drug distribution. Oral contraceptive use should also be considered[36]

Treatment adherence

Adherence to appointments and treatment, particularly oral medications, can be problematic in AYA patients and lead to worsening of side effects, poorer outcomes[52] and delayed diagnosis of metastasis or local recurrence resulting in the need for additional treatment[53]. It must be noted that non-adherence, as with many aspects of AYA care, is likely to be multifactorial and not completely understood[54][55]. Faced with requiring often intensive cancer treatment AYA patients may feel pressured into making decisions that they may not be mature enough to yet[56]. In breast cancer patients younger age has been shown to be a predictor of poor adherence to adjuvant endocrine therapy[57].

In order to improve adherence an understanding of the reasons for non-adherence is imperative. Family relationships, treatment setting and treatment intensity are all likely to play apart. Distress is a prevalent association of poor concordance [54]. A non-judgemental approach should be used by health care professionals in order to address issues and renegotiate ongoing care plans together. Clinicians should 'pick their battles' reserving them for the most important issues only. By doing this the AYA patient may feel they are able to maintain a level of control over their care rather than being dictated to[58]. Recognition of the "sex and drugs and rock 'n' roll" lifestyle[59] of this age group is essential and providing a degree of flexibility in treatment plans enables AYA patients to maintain some normality in their lives, without hindering their outcomes[56]. Family cohesion should be encouraged [60]whilst enabling the patient to maintain some autonomy. The use of a video game intervention has been shown to improve adherence in 13-29 year olds[61], indicating that age-appropriate means of engagement and education have important roles.

Clinical Trial Recruitment

Clinical trials are often seen as the gold standard of care, leading to enhanced treatment for both those in trials and those receiving care at the same institution[62]. Poor inclusion rates in cancer clinical trials have historically been associated with the lag in survival improvements in AYA [63]. Participation rates for AYAs ranges from 5-34% compared to over 90% in children[63][64][65]. The European paediatric Soft tissue sarcoma Study Group (EpSSG) compared the proportion of AYA patients (15-19 year olds) with the proportion of children (0-14 year olds) treated in EpSSG clinical trials based upon incidence and population rates. They noted the observed to expected ratio to be 0.30 for AYAs compared to 0.64 for children, though this varied between subtypes[66]. In an attempt to rectify these poor accrual rates there has been a push to improve involvement of AYAs in clinical trials focusing on 5 key areas; appropriateness, availability, accessibility, awareness, and acceptability to patients[67].

The appropriateness of trials refers to the age inclusion criterion, which is often arbitrary and reflective of the clinical practices of trial designers as opposed to having scientific basis[67]. This means that AYA patients are often excluded from paediatric trials for being too old or from adult ones for not being old enough[68]. Recent shifts have shown adjustments of age criteria to enable AYA participation, for example, the lower age for adult trials being lowered to 16 years in all cancer trials and the upper age limit of paediatric trials increasing to 21-25 years for brain tumours and sarcomas[67]. Age range should reflect the group of patients where the biology of the cancer makes the study question relevant. As age ranges become wider there may be confusion over which trials AYA patients should be entered into meaning better collaboration between adult and paediatric oncologists is required[69].

Availability of trials may be limited due to organisational and service boundaries such as having the relevant personnel at a treatment centre to open a trial and the age of patients that services are funded

to treat. In addition, the availability of new agents is often limited in this patient population due to a lack of preclinical research and poor funding from drug companies. The rarity of cancers in AYA patients often requires international collaboration to obtain sufficient trial numbers which adds to the financial burden. Trials such as the EUROMOS-1 trial or Euro-Ewings trial series show it possible to overcome the barriers faced.

Trial regulations which have the purpose of protecting minors, particularly in Phase 1 and 2 clinical trials can actually hinder access to potentially beneficial treatments. The ACCELERATE platform is a multi-stake-holder platform founded by the Cancer Drug Development Forum, SIOPE and Innovative Therapies for Children with Cancer (ITCC) European network which aims to accelerate innovation for children and adolescents with cancer[70]. Strategies for doing this include reducing trial entry to 12 years of age for phase 2 trials and allowing adolescents to participate in Phase 1 trials where there is scientific rationale and potential therapeutic benefit such as the presence of a drug target.

Patient acceptability of the trial is paramount and thought needs to be given to this particularly if it involves additional hospital visits or investigations. Involvement of AYA patients and their families in trial design may improve this barrier[71].

Cancer clinicians outside of tertiary centres and with limited experience in the rare cancers seen in AYA patients may be unaware of relevant clinical trials, cautious of treating patients with the dose intensity required or simply may not have access to them. There therefore needs to be an increased awareness of the importance of referring AYA patients into specialist centres.

Path to cancer diagnosis

AYA patients often report a prolonged path to diagnosis which may impact on their potential for cure. A Danish retrospective cohort study looked at the primary care use of AYAs during the two years preceding a cancer diagnosis and found an increase in primary care use 16 months prior to cancer diagnosis which increased exponentially 8 months before diagnosis[72]. The timing of the increase was dependant on tumour type: 17 months for CNS tumours, 12 months for sarcomas, 9 months for lymphomas, 5 to 6 months for germ cell tumours, bone tumours and leukaemias and 3 months for malignant melanomas. An increase in the number of blood tests performed was also seen from 11 months[72]. A British study found that cancer patients aged 16-25 years were twice as likely as older patients to have three or more GP consultations before referral for diagnostic tests[73]. It is therefore not the case that AYAs are not reporting their signs and symptoms but either that what they are reporting is vague and non-specific, or that clinicians are not acting promptly upon specific symptoms because they consider the probability of serious disease to be low. AYA cancers are rare and in a patient presenting four or more times the absolute risk of a patient having cancer is still only 1.8 per 10,000[74]. Zhou and colleagues recently found that in the UK fast-track cancer referrals were less likely to be made for cancers that present with non-specific symptoms and for low cancer incidence demographic groups[75]. AYAs are also thought to be less likely to pursue medical attention once they have been reassured about their symptoms compared to adults or the parents of unwell children[76], this may mean AYA require a distinct safety-netting procedure to adults[77]. In the UK, guidelines on managing patients attending multiple times with the same problem have been produced and fast track diagnostic pathways put in place in an attempt to combat long pathways to diagnoses[78] which can impact on survival[79]. Cancer awareness programmes aimed at AYA patients are also important to encourage reporting of early symptoms[80].

Palliative care and end of life care

Palliative care skills should be recruited to enhance supportive care and are equally as important for patients being treated with curative intent as those being treated with palliative intent. Introducing palliative care services at the beginning of treatment will enable patients and their families to build relationships with the team, reducing the feeling of abandonment some patients feel when they finish active treatment because life is expected to be short even if treatment continues.

Palliative care should be provided by healthcare professionals who have expertise in the complex needs of AYA patients and become part of a patient's comprehensive care. It is crucial that care teams don't assume that patients are unwilling to discuss end of life issues because of their age [81]. Lyon et al. found that having end of life discussions with patients and their families lead to greater congruity between what the adolescent wanted and what the families thought they would want[82]. A retrospective study found that half of end of life discussions were initiated in the last 30 days of life allowing minimal time for end of life preparation[83]. In this study more than half of the patients died in hospital despite findings that patients prefer to die at home. Half of these patients died on ICU which may reflect that the tipping point from being fit with a good quality of life and able to tolerate active treatment to being very unwell in the last few days of life often rapidly occurs in young patients, making planning while health is still good very important. Exploring individual preferences for the discussion of end of life care may be crucial to improving patient experiences. An exploratory study of 50 patients found adolescents willing to discuss end of life decision making using a personal survey[84].

Cancer survivorship and late effects

An increase in survival rates from AYA cancers brings a greater population of survivors living with the long-term effects of their cancer. AYA patients experience their own pattern of late effects influenced by their physiology, the cancers they develop and the treatment they receive[85]. These undoubtedly have an impact on the quality of life of survivors and financial costs for health services[86]. PanCare, a multidisciplinary pan-European network made up of healthcare professionals, survivors and family member, aims to reduce the frequency, severity and impact of late side-effects of children and adolescents with cancer.

Second Primary Cancers

AYA survivors have a significant risk of developing second primary malignancies compared to both the general population[87] and older patients with cancer[88]. As well as individual factors such as genetics, co-morbidities and lifestyle an individuals risk of a second malignancy is affected by a number of things including; age at diagnosis, site of original cancer and treatment received[88]. Testicular cancer survivors treated with alkylating agents and topoisomerase II inhibitors have been found to be at an increased risk of developing acute myeloid leukaemia[89][90]. These patients are also at a significantly increased risk of developing contralateral testicular cancer, malignant mesothelioma, and cancers of the lung and gastrointestinal tract[91]. Radiotherapy exposure has been shown to result in malignancies of the skin and carcinomas of the thyroid, bone, breast and brain[92].

Cardiovascular

Cardiovascular complications are the commonest non-malignant cause of death in cancer survivors[93]. Anthracyclines increase an individuals risk of left ventricular dysfunction, cardiomyopathy and

dysrhythmias. Cisplatin based chemotherapy regimes have been shown to cause long-term cardiovascular complications in testicular cancer survivors[94][95]. Radiotherapy can also result in cardiomyopathy, pericardial fibrosis and pericarditis, heart valve abnormalities, conduction disorders and coronary, carotid and subclavian artery disease[92].

Other

Pulmonary toxicity can arise from alkylating agents and radiotherapy[96]. Patients treated with Bleomycin need to be educated of the possible risk of toxicity from oxygen therapy and the appropriate warnings placed on their medical records. Ifosfamide, methotrexate, platinum agents and radiotherapy can all lead to impairment of renal function and the urinary tract[97]. Endocrine complications include abnormalities of thyroid function and pituitary dysfunction and alterations in glucose metabolism[98]. Long term neurological complications from cisplatin based chemotherapy include hearing impairments and Raynaud's phenomena[95].

Late psychosocial effects

Socioeconomic late effects of AYA cancers can have a huge impact on a survivors quality of life and should not be overlooked.[99] The adolescent and young adult period of life covers the time when individuals are finishing school, embarking on careers or higher education and developing emotional and sexual relationships. It is the time when young people are starting to leave the family home and develop financial independence. A cancer diagnosis during this time can therefore delay or prevent these processes of achieving autonomy.

Cancer survivors are less likely to be married, be living independently, have attained post-secondary school education and be working full time than their siblings[100]. Financial difficulties are also reported[99]. Anxiety, stress and depression are prevalent in AYA cancer survivors[101].

Neurocognitive delay, both developmental and functional is a lasting complication in patients treated for AYA cancers [100] and can influence an individuals performance at work or in education. AYA patients have reported that cancer has a negative impact on both their career and education plans[102]. Some however reconstruct this disruption in a positive light and use it as an opportunity to refocus on their future and individual goals[102]. Experienced teams may be able to promote this approach.

Perception of body image can change as a result of cancer lowering self-esteem in a population where appearance is often important. Surgical scars, hair loss, loss of body parts can cause AYAs to feel less attractive and hinder their ability to form relationships with peers and start sexual relationships[103][99]. The risk of infertility and cancer recurrence can also make AYAs more cautious about entering meaningful relationships.

Fertility

Both cancer and its treatment can reduce a patients fertility[92][104]. As survival rates improve more and more patients are having to deal with this consequence in later life. The risk to a patient depends on the treatment they receive. Chemotherapy regimes containing Alkylating agents are harmful to the ovaries and testes. Pelvic radiotherapy can cause oligospermia or azoospermia and ovarian and uterine dysfunction[92]. High dose cranial radiotherapy can reduce fertility by impairing hypothalamic pituitary

function. Fertile Hope have developed a risk calculator based on clinical experience and published research to aid with the decision-making process[105].

AYA patients may never have considered having children and therefore discussions about fertility preservation could be unexpected and "embarrassing", inhibiting discussion by professionals who are not regularly practiced in conducting them. Despite this it remains a crucial topic to address and one which may become a source of resentment later on if incompletely or self-consciously discussed. Studies have shown a willingness amongst patients and their parents to discuss fertility options as long as it does not delay treatment[106]. A study of male cancer patients found sperm cryopreservation to have a positive emotional impact during treatment[107], possibly as it implies a normal future.

Clinicians should provide AYA patients with comprehensive and current information about fertility preservation at the time of diagnosis to enable them to make the required decisions. This is not an easy task, particularly where female patients are concerned, and requires healthcare professionals keeping up to date with an ever-changing field. There is therefore undoubtedly a need for clinical practice guidelines, education of healthcare professionals and inclusion of fertility experts in the care team of AYA patients.

It should be noted that AYA patients should be educated on the importance of practising safe sex despite potentially reduced fertility in order to prevent sexually transmitted diseases and unplanned pregnancies[104][92].

Long term follow up and education

It is important that AYA survivors are aware of the potential complications that they may face in later life as a result of their treatment and that they are supported in modifying simple lifestyle factors such as diet, exercise and smoking cessation in order to reduce their risk. Modern day approaches to building relationships with peer survivors and promoting healthy behaviours include the use of social media[108] and blogs[109].

Ongoing clinical review in AYA cancer survivors is necessary to identify recurrence, late effects and provide reassurance[110]. It is therefore crucial that AYA clinicians implement the appropriate surveillance strategy and promote awareness of the risk of late effects amongst community healthcare providers. To support this the Children's Oncology Group (COG) have produced expert consensus guidelines for the long term follow up of younger AYA survivors[92]. PanCare are also adding an evidence base and newly completed UK cohort studies of late effects specific to AYA have great promise[111]. Risk stratification of AYA cancer survivors according to their risk of developing late effects enables patients to be followed up appropriately for example those at lower risk in the community versus those at higher risk by their specialist centre. New schemes are in place that enable patients to be followed up remotely by specialist teams without the need for hospital visits[112]. This not only promotes self-care, it reduces the burden on outpatient services and reduces the disruption on a patient's life, helping them to return to some normality.

<u>Conclusion</u>

The identification of AYA patients as a group with a unique set of requirements has led to a burst of associated research. Trama et al. have demonstrated that this is working to reduce the survival gap but that further progress is still required. Undoubtedly many questions remain unanswered and needs

remain apparent. The James Lind Alliance in the UK have recently published a list of ten research priorities which they devised after consultation with patients, family members and health care professionals[113]. The aim is to encourage and inspire work which will lead to improvements in outcomes and experiences of AYA patients and their families.

Collaborations and networks between patients, charities (e.g. Teenage Cancer Trust, Canteen and Teen Cancer America), professionals (e.g. SIOPE and ESMO) and organisations (e.g. Teenagers and Young Adults with Cancer and SIAMO) are bringing together expert knowledge and experience from across the globe facilitating progress in even the rarer cancers. The hope is that AYA oncology will continue to be an advancing field over the coming years.

References

[1] Sawyer SM, Azzopardi P, Wickremarathne D, Patton G. The age of adolescence. Lancet Child Adolesc 2018. http://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(18)30022-1/fulltext.

[2] Gatta G, Zigon G, Capocaccia R, Coebergh JW, Desandes E, Kaatsch P, et al. Survival of European children and young adults with cancer diagnosed 1995-2002. Eur J Cancer 2009;45:992–1005. doi:10.1016/j.ejca.2008.11.042.

[3] World Health Organization - Health Topics. Adolescent Health. n.d. http://www.who.int/topics/adolescent_health/en/ (accessed January 24, 2018).

[4] Barr RD, Ferrari A, Ries L, Whelan J, Bleyer WA. Cancer in Adolescents and Young Adults. JAMA Pediatr 2016;170:495. doi:10.1001/jamapediatrics.2015.4689.

[5] Stark D, Bielack S, Brugieres L, Dirksen U, Duarte X, Dunn S, et al. Teenagers and young adults with cancer in Europe: From national programmes to a European integrated coordinated project. Eur J Cancer Care (Engl) 2016;25:419–27. doi:10.1111/ecc.12365.

[6] Department of Health and Human Services, National Institutes of Health NCI. Closing the gap: research and care imperatives for adolescents and young adults with cancer: a report of the Adolescent and Young Adult Oncology Progress Review Group 2006.

[7] Desandes E, Stark DP. Epidemiology of Adolescents and Young Adults with Cancer in Europe, 2016, p. 1–15.

[8] Pesola F, Ferlay J, Sasieni P. Cancer incidence in English children, adolescents and young people: past trends and projections to 2030. Br J Cancer 2017. doi:10.1038/bjc.2017.341.

[9] Bleyer A, Viny A, Barr R. E pidemiology , A ccess , and O utcomes : SEER S eries Cancer in 15- to 29-Year-Olds by Primary Site. Oncologist 2006;11:590–601. doi:10.1634/theoncologist.11-6-590.

[10] Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: Data from the surveillance, epidemiology, and end results program. Cancer 2009;115:1531–43. doi:10.1002/cncr.24121.

[11] Bleyer A, O'Leary M, Barr R RL (Eds). SEER Cancer Epidemiology in Older Adolescents and Young Adults 15-29 Years of Age. Cancer Epidemiol Older Adolesc Young Adults 15 to 29 Years Age, Incl SEER Incid Surviv 1975-2000 2006:53–73.

[12] Trama A, Botta L, Foschi R, Ferrari A, Stiller C, Desandes E, et al. Survival of European adolescents and young adults diagnosed with cancer in 2000–07: population-based data from EUROCARE-5. Lancet Oncol 2016;17:896–906. doi:10.1016/S1470-2045(16)00162-5.

[13] Tricoli J V., Blair DG, Anders CK, Bleyer WA, Boardman LA, Khan J, et al. Biologic and clinical characteristics of adolescent and young adult cancers: Acute lymphoblastic leukemia, colorectal cancer, breast cancer, melanoma, and sarcoma. Cancer 2016;122:1017–28. doi:10.1002/cncr.29871.

[14] Menzies AM, Haydu LE, Visintin L, Carlino MS, Howle JR, Thompson JF, et al. Distinguishing clinicopathologic features of patients with V600E and V600K BRAF-mutant metastatic melanoma. Clin Cancer Res 2012;18:3242–9. doi:10.1158/1078-0432.CCR-12-0052.

[15] Partridge AH, Hughes ME, Warner ET, Ottesen RA, Wong YN, Edge SB, et al. Subtype-dependent relationship between young age at diagnosis and breast cancer survival. J Clin Oncol 2016;34:3308–14. doi:10.1200/JCO.2015.65.8013.

[16] Möricke A, Zimmermann M, Reiter A, Gadner H, Odenwald E, Harbott J, et al. Prognostic Impact of Age in Children and Adolescents with Acute Lymphoblastic Leukemia: Data from the Trials ALL-BFM 86, 90, and 95. Klin Pädiatrie 2005;217:310–20. doi:10.1055/s-2005-872515.

[17] Sultan I, Qaddoumi I, Yaser S, Rodriguez-Galindo C, Ferrari A. Comparing adult and pediatric rhabdomyosarcoma in the surveillance, epidemiology and end results program, 1973 to 2005: An analysis of 2,600 patients. J Clin Oncol 2009;27:3391–7. doi:10.1200/JCO.2008.19.7483.

[18] Lagarde P, Przybyl J, Brulard C, Pérot G, Pierron G, Delattre O, et al. Chromosome instability accounts for reverse metastatic outcomes of pediatric and adult synovial sarcomas. J Clin Oncol 2013;31:608–15. doi:10.1200/JCO.2012.46.0147.

[19] Kohsaka S, Shukla N, Ameur N, Ito T, Ng CKY, Wang L, et al. A recurrent neomorphic mutation in MYOD1 defines a clinically aggressive subset of embryonal rhabdomyosarcoma associated with PI3K-AKT pathway mutations. Nat Genet 2014;46:595–600. doi:10.1038/ng.2969.

[20] Smith S, Mooney S, Cable M, Taylor RM, Cable M, Mooney S, et al. THE BLUEPRINT for teenagers and young n.d.

[21] Ferrari A, Thomas D, Franklin ARK, Hayes-Lattin BM, Mascarin M, van der Graaf W, et al. Starting an Adolescent and Young Adult Program: Some Success Stories and Some Obstacles to Overcome. J Clin Oncol 2010;28:4850–7. doi:10.1200/JCO.2009.23.8097.

[22] Jones LJW, Pini SA, Morgan SJ, Birk GK, Stark DP. How Do Teenagers and Young Adults with Cancer Experience Their Care? A European Survey. J Adolesc Young Adult Oncol 2017;6:102–10. doi:10.1089/jayao.2016.0011.

[23] Stark D, Bowen D, Dunwoodie E, Feltbower R, Johnson R, Moran A, et al. Survival patterns in teenagers and young adults with cancer in the United Kingdom: Comparisons with younger and older age groups. Eur J Cancer 2015;51:2643–54. doi:10.1016/j.ejca.2015.08.010.

[24] Stark D, Lewis I. Improving Outcomes for Teenagers and Young Adults (TYA) with Cancer. Klin Pädiatrie 2013;225:331–4. doi:10.1055/s-0033-1358392.

[25] Kent EE, Smith AW, Keegan THM, Lynch CF, Wu X-C, Hamilton AS, et al. Talking About Cancer and Meeting Peer Survivors: Social Information Needs of Adolescents and Young Adults Diagnosed

with Cancer. J Adolesc Young Adult Oncol 2013;2:44–52. doi:10.1089/jayao.2012.0029.

[26] Whiteson M. The Teenage Cancer Trust—advocating a model for teenage cancer services. Eur J Cancer 2003;39:2688–93. doi:10.1016/j.ejca.2003.08.023.

[27] BRIGHTLIGHT n.d. http://www.brightlightstudy.com/ (accessed December 13, 2017).

[28] Ferrari A, Veneroni L, Clerici CA, Casanova M, Chiaravalli S, Magni C, et al. Clouds of Oxygen: Adolescents With Cancer Tell Their Story in Music. J Clin Oncol 2015;33:218–21. doi:10.1200/JCO.2014.57.9888.

[29] Hayes-Lattin B, Mathews-Bradshaw B, Siegel S. Adolescent and young adult oncology training for health professionals: A position statement. J Clin Oncol 2010;28:4858–61. doi:10.1200/JCO.2010.30.5508.

[30] Taylor RM, Feltbower RG, Aslam N, Raine R, Whelan JS, Gibson F. Modified international e-Delphi survey to define healthcare professional competencies for working with teenagers and young adults with cancer. BMJ Open 2016;6:e011361. doi:10.1136/bmjopen-2016-011361.

[31] Committee. LFR. LIVESTRONG YOUNG ADULT ALLIANCE IMPLEMENTATION PLAN. Austin, USA: 2014.

[32] ESMO/SIOPE Adolescents and Young Adults Working Group. The goal of the joint Working Group on Cancer in Adolescents and Young Adults (AYA) is to promote education in cancer topics specific to this population. Eur Soc Med Oncol n.d. http://www.esmo.org/About-Us/Who-We-Are/Educational-Committee/Adolescents-and-Young-Adults-Working-Group (accessed January 24, 2018).

[33] Ercan O, Alikasifoglu M, Erginoz E, Janda J, Kabicek P, Rubino A, et al. Demography of adolescent health care delivery and training in Europe. Eur J Pediatr 2009;168:417–26. doi:10.1007/s00431-008-0759-1.

[34] Ramphal R, D'Agostino N, Klassen A, McLeod M, De Pauw S, Gupta A. Practices and Resources Devoted to the Care of Adolescents and Young Adults with Cancer in Canada: A Survey of Pediatric and Adult Cancer Treatment Centers. J Adolesc Young Adult Oncol 2011;1:140–4. doi:10.1089/jayao.2011.0023.

[35] Perales M-A, Drake EK, Pemmaraju N, Wood WA. Social Media and the Adolescent and Young Adult (AYA) Patient with Cancer. Curr Hematol Malig Rep 2016;11:449–55. doi:10.1007/s11899-016-0313-6.

[36] Veal GJ, Hartford CM, Stewart CF. Clinical pharmacology in the adolescent oncology patient. J Clin Oncol 2010;28:4790–9. doi:10.1200/JCO.2010.28.3473.

[37] Ramanujachar R, Richards S, Hann I, Goldstone A, Mitchell C, Vora A, et al. Adolescents with acute lymphoblastic leukaemia: Outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. Pediatr Blood Cancer 2007;48:254–61. doi:10.1002/pbc.20749.

[38] Boissel N, Auclerc MF, Lhéritier V, Perel Y, Thomas X, Leblanc T, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol 2003;21:774–80. doi:10.1200/JCO.2003.02.053.

[39] de Bont JM, van der Holt B, Dekker AW, van der Does-van den Berg A, Sonneveld R, Pieters R.

Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands [1]. Leukemia 2004;18:2032–5. doi:10.1038/sj.leu.2403538.

[40] Stock W, La M, Sanford B, Bloomfield CD, Vardiman JW, Gaynon P, et al. AYA ALL - CCG vs CALGB. Young 2008;112:1646–54. doi:10.1182/blood-2008-01-130237.The.

[41] Usvasalo A, Räty R, Knuutila S, Vettenranta K, Harila-Saari A, Jantunen E, et al. Acute lymphoblastic leukemia in adolescents and young adults in Finland. Haematologica 2008;93:1161–8. doi:10.3324/haematol.12466.

[42] Hallböök H, Gustafsson G, Smedmyr B, Söderhäll S, Heyman M. Treatment outcome in young adults and children > 10 year of age with acute lymphoblastic leukemia in Sweden: A comparison between a pediatric protocol and an adult protocol. Cancer 2006;107:1551–61. doi:10.1002/cncr.22189.

[43] Grundy P, Rae C, Marr K, Gupta S. (Abstract) Epidemiology of adolescent and young adult cancer in Canada: Incidence, Prevalence and Relative Survival. 2nd Glob. Adolesc. Young Adult Cancer Congr., Atlanta, GA, USA: 2017.

[44] Collins M, Wilhelm M, Conyers R, Herschtal A, Whelan J, Bielack S, et al. Benefits and adverse events in younger versus older patients receiving neoadjuvant chemotherapy for osteosarcoma: Findings from a meta-analysis. J Clin Oncol 2013;31:2303–12. doi:10.1200/JCO.2012.43.8598.

[45] Juergens C, Weston C, Lewis I, Whelan J, Paulussen M, Oberlin O, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatr Blood Cancer 2006;47:22–9. doi:10.1002/pbc.20820.

[46] Dasgupta R, Indelicato DJ, Hawkins DS. NIH Public Access 2014;118:1130–7. doi:10.1002/cncr.26358.Patterns.

[47] Khamly KK, Thursfield VJ, Fay M, Desai J, Toner GC, Choong PFM, et al. Gender-specific activity of chemotherapy correlates with outcomes in chemosensitive cancers of young adulthood. Int J Cancer 2009;125:426–31. doi:10.1002/ijc.24376.

[48] Klimm B, Reineke T, Haverkamp H, Behringer K, Eich HT, Josting A, et al. Role of hematotoxicity and sex in patients with Hodgkin's lymphoma: An analysis from the German Hodgkin Study Group. J Clin Oncol 2005;23:8003–11. doi:10.1200/JCO.2005.205.60.

[49] Huguet F, Leguay T, Raffoux E, Thomas X, Beldjord K, Delabesse E, et al. Pediatric-inspired therapy in adults with philadelphia chromosome-negative acute lymphoblastic leukemia: The GRAALL-2003 study. J Clin Oncol 2009;27:911–8. doi:10.1200/JCO.2008.18.6916.

[50] Bleyer A. Young adult oncology: the patients and their survival challenges. CA Cancer J Clin n.d.;57:242–55.

[51] Roscoe JA, Morrow GR, Aapro MS, Molassiotis A, Olver I. Anticipatory nausea and vomiting. Support Care Cancer 2011;19:1533–8. doi:10.1007/s00520-010-0980-0.

[52] Relling M V, Hancock ML, Boyett JM, Pui C-H, Evans WE. Prognostic importance of 6-mercaptopurine dose intensity in acute lymphoblastic leukemia. Blood 1999;93:2817–23.

[53] Williams K. Adolescent and Young Adult Oncology. Clin J Oncol Nurs 2013.

[54] Butow P, Palmer S, Pai A, Goodenough B, Luckett T, King M. Review of adherence-related issues in adolescents and young adults with cancer. J Clin Oncol 2010;28:4800–9. doi:10.1200/JCO.2009.22.2802.

[55] Kondryn HJ, Edmondson CL, Hill J, Eden TOB. Treatment non-adherence in teenage and young adult patients with cancer. Lancet Oncol 2011;12:100–8. doi:10.1016/S1470-2045(10)70069-3.

[56] Taddeo D, Egedy M, Frappier J-Y. Adherence to treatment in adolescents. Paediatr Child Health 2008;13:19–24. doi:19119348.

[57] Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: A systematic review. Breast Cancer Res Treat 2012;134:459–78. doi:10.1007/s10549-012-2114-5.

[58] Sawyer SM, Aroni R a. Self-management in adolescents with chronic illness. What does it mean and how can it be acheived? Med J Aust 2005;183:405–9.

[59] Morgan S, Davies S, Palmer S, Plaster M. Sex, Drugs, and Rock “n” Roll: Caring for Adolescents and Young Adults With Cancer. J Clin Oncol 2010;28:4825–30. doi:10.1200/JCO.2009.22.5474.

[60] DiMatteo MR. The role of effective communication with children and their families in fostering adherence to pediatric regimens. Patient Educ Couns 2004;55:339–44. doi:10.1016/j.pec.2003.04.003.

[61] Kato PM, Cole SW, Bradlyn AS, Pollock BH. A Video Game Improves Behavioral Outcomes in Adolescents and Young Adults With Cancer: A Randomized Trial. Pediatrics 2008;122:e305–17. doi:10.1542/peds.2007-3134.

[62] Downing A, Morris EJA, Corrigan N, Sebag-Montefiore D, Finan PJ, Thomas JD, et al. High hospital research participation and improved colorectal cancer survival outcomes: A population-based study. Gut 2017;66:89–96. doi:10.1136/gutjnl-2015-311308.

[63] Bleyer W a, Tejeda H, Murphy SB, Robison LL, Ross J a, Pollock BH, et al. National cancer clinical trials: Children have equal access; Adolescents do not. J Adolesc Heal 1997;21:366–73. doi:10.1016/s1054-139x(97)00110-9.

[64] Burke ME, Albritton K, Marina N. Challenges in the recruitment of adolescents and young adults to cancer clinical trials. Cancer 2007;110:2385–93. doi:10.1002/cncr.23060.

[65] Tai E, Buchanan N, Eliman D, Westervelt L, Beaupin L, Lawvere S, et al. Understanding and Addressing the Lack of Clinical Trial Enrollment Among Adolescents With Cancer. Pediatrics 2014;133:S98–103. doi:10.1542/peds.2014-0122D.

[66] Ferrari A, Trama A, De Paoli A, Bergeron C, Merks JHM, Jenney M, et al. Access to clinical trials for adolescents with soft tissue sarcomas: Enrollment in European pediatric Soft tissue sarcoma Study Group (EpSSG) protocols. Pediatr Blood Cancer 2017;64:e26348. doi:10.1002/pbc.26348.

[67] Fern LA, Lewandowski JA, Coxon KM, Whelan J. Available, accessible, aware, appropriate, and acceptable: A strategy to improve participation of teenagers and young adults in cancer trials. Lancet Oncol 2014;15:e341–50. doi:10.1016/S1470-2045(14)70113-5.

[68] Ferrari A, Aricò M, Dini G, Rondelli R, Porta F. Upper Age Limits for Accessing Pediatric Oncology

Centers in Italy: A Barrier Preventing Adolescents with Cancer from Entering National Cooperative AIEOP Trials. Pediatr Hematol Oncol 2012;29:55–61. doi:10.3109/08880018.2011.572963.

[69] Felgenhauer J, Hooke MC. Regulatory barriers to clinical trial enrollment of adolescent and young adult oncology patients. Pediatrics 2014;133 Suppl:S119-22. doi:10.1542/peds.2014-0122H.

[70] Pearson ADJ, Herold R, Copland C, Bradley-garelik B, Binner D, Capdeville R, et al. Implementation of mechanism of action biology-driven early drug development for children with cancer. Eur J Cancer 2016;62:124–31. doi:10.1016/j.ejca.2016.04.001.

[71] Fern L, Davies S, Eden T, Feltbower R, Grant R, Hawkins M, et al. Rates of inclusion of teenagers and young adults in England into National Cancer Research Network clinical trials: Report from the National Cancer Research Institute (NCRI) Teenage and Young Adult Clinical Studies Development Group. Br J Cancer 2008;99:1967–74. doi:10.1038/sj.bjc.6604751.

[72] Ahrensberg JM, Fenger-Grøn M, Vedsted P. Primary care use before cancer diagnosis in adolescents and young adults - A nationwide register study. PLoS One 2016;11:5–6. doi:10.1371/journal.pone.0155933.

[73] Ferrari A, Miceli R, Casanova M, Meazza C, Favini F, Luksch R, et al. The symptom interval in children and adolescents with soft tissue sarcomas. Cancer 2010;116:177–83. doi:10.1002/cncr.24695.

[74] Dommett RM, Redaniel MT, Stevens MCG, Hamilton W, Martin RM. Features of cancer in teenagers and young adults in primary care: A population-based nested case-control study. Br J Cancer 2013;108:2329–33. doi:10.1038/bjc.2013.191.

[75] Zhou Y, Mendonca SC, Abel GA, Hamilton W, Walter FM, Johnson S, et al. Variation in “fast-track” referrals for suspected cancer by patient characteristic and cancer diagnosis: evidence from 670 000 patients with cancers of 35 different sites. Br J Cancer 2018;118:24–31. doi:10.1038/bjc.2017.381.

[76] Fern LA, Birch R, Whelan J, Cooke M, Sutton S, Neal RD, et al. Why can’t we improve the timeliness of cancer diagnosis in children, teenagers, and young adults? BMJ 2013;347:f6493–f6493. doi:10.1136/bmj.f6493.

[77] Dommett R et al. Too Young to Get Cancer. Accelerate, Coordinate, Evaluate (ACE) Programme An early diagnosis of cancer initiative supported by: NHS England, Cancer Research UK and Macmillan Cancer Support. n.d. https://www.cancerresearchuk.org/sites/default/files/ace_vague_symptoms_report_final_v1.1.pdf (accessed January 24, 2018).

[78] National Institute for Health and Care Excellence. Suspected cancer: recognition and referral. NICE guideline (NG12). 2017. https://www.nice.org.uk/guidance/ng12 (accessed December 12, 2017).

[79] Ferrari A, Lo Vullo S, Giardiello D, Veneroni L, Magni C, Clerici CA, et al. The Sooner the Better? How Symptom Interval Correlates With Outcome in Children and Adolescents With Solid Tumors: Regression Tree Analysis of the Findings of a Prospective Study. Pediatr Blood Cancer 2016;63:479–85. doi:10.1002/pbc.25833.

[80] Magni C, Segrè C, Finzi C, Veneroni L, Clerici CA, Massimino M, et al. Adolescents’ Health

Awareness and Understanding of Cancer and Tumor Prevention: When and Why an Adolescent Decides to Consult a Physician. Pediatr Blood Cancer 2016;63:1357–61. doi:10.1002/pbc.25985.

[81] Wein S, Pery S, Zer A. Role of palliative care in adolescent and young adult oncology. J Clin Oncol 2010;28:4819–24. doi:10.1200/JCO.2009.22.4543.

[82] Lyon ME, Jacobs S, Briggs L, Cheng YI, Wang J. Family-Centered Advance Care Planning for Teens With Cancer. JAMA Pediatr 2013;167:460. doi:10.1001/jamapediatrics.2013.943.

[83] Bell CJ, Skiles J, Pradhan K, Champion VL. End-of-life experiences in adolescents dying with cancer. Support Care Cancer 2010;18:827–35. doi:10.1007/s00520-009-0716-1.

[84] Lyon ME, Mccabe MA, Patel KM, D'Angelo LJ. What do adolescents want? An exploratory study regarding end-of-life decision-making. J Adolesc Heal 2004;35:1–6. doi:10.1016/j.jadohealth.2004.02.009.

[85] Woodward E, Jessop M, Glaser A, Stark D. Late effects in survivors of teenage and young adult cancer: Does age matter? Ann Oncol 2011;22:2561–8. doi:10.1093/annonc/mdr044.

[86] Richardson DP, Daly C, Sutradhar R, Paszat LF, Wilton AS, Rabeneck L, et al. Hospitalization rates among survivors of young adult malignancies. J Clin Oncol 2015;33:2655–9. doi:10.1200/JCO.2014.60.1914.

[87] National Cancer Institute NPN 05-5302. New malignacies among cancer survivors: SEER Cancer Registries, 1973-2000. Bethesda, MD; 2006.

[88] Lee JS, Dubois SG, Coccia PF, Bleyer A, Olin RL, Goldsby RE. Increased risk of second malignant neoplasms in adolescents and young adults with cancer. Cancer 2016;122:116–23. doi:10.1002/cncr.29685.

[89] Wierecky J, Kollmannsberger C, Boehlke I, Kuczyk M, Schleicher J, Schleucher N, et al. Secondary leukemia after first-line high-dose chemotherapy for patients with advanced germ cell cancer. J Cancer Res Clin Oncol 2005;131:255–60. doi:10.1007/s00432-004-0628-x.

[90] Howard R, Gilbert E, Lynch CF, Hall P, Storm H, Holowaty E, et al. Risk of Leukemia Among Survivors of Testicular Cancer: A Population-based Study of 42,722 Patients. Ann Epidemiol 2008;18:416–21. doi:10.1016/j.annepidem.2008.01.003.

[91] Travis LB, Beard C, Allan JM, Dahl AA, Feldman DR, Oldenburg J, et al. Testicular cancer survivorship: Research strategies and recommendations. J Natl Cancer Inst 2010;102:1114–30. doi:10.1093/jnci/djq216.

[92] Children's Oncology Group. Guidelines for Survivors of Childhood , Adolescent , and Young Adult Cancer Long-Term Follow-Up Guidelines, Version 4.0 2013:1–241.

[93] Chen MH, Colan SD, Diller L. Cardiovascular disease: Cause of morbidity and mortality in adult survivors of childhood cancers. Circ Res 2011;108:619–28. doi:10.1161/CIRCRESAHA.110.224519.

[94] Haugnes HS, Wethal T, Aass N, Dahl O, Klepp O, Langberg CW, et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: A 20-year follow-up study. J Clin Oncol 2010;28:4649–57. doi:10.1200/JCO.2010.29.9362.

[95] Abouassaly R, Fossa SD, Giwercman A, Kollmannsberger C, Motzer RJ, Schmoll HJ, et al. Sequelae of treatment in long-term survivors of testis cancer. Eur Urol 2011;60:516–26.

doi:10.1016/j.eururo.2011.05.055.

[96] Mulder RL, Thonissen NM, van der Pal HJH, Bresser P, Hanselaar W, Koning CCE, et al. Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer. Thorax 2011;66:1065–71. doi:10.1136/thoraxjnl-2011-200618.

[97] Jones deborah P, Spunt SL, Green D, Springate JE. Renal late effects in patients treated for cancer in childhood: A report from the Children's Oncology Group. Pediatr Blood Cancer 2008;51:724–31. doi:10.1002/pbc.21695.

[98] Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. Endocr Relat Cancer 2010;17:141–59. doi:10.1677/ERC-10-0002.

[99] Warner EL, Kent EE, Trevino KM, Parsons HM, Zebrack BJ, Kirchhoff AC. Social well-being among adolescents and young adults with cancer: A systematic review. Cancer 2016;122:1029–37. doi:10.1002/cncr.29866.

[100] Prasad PK, Hardy KK, Zhang N, Edelstein K, Srivastava D, Zeltzer L, et al. Psychosocial and neurocognitive outcomes in adult survivors of adolescent and early young adult cancer: A report from the Childhood Cancer Survivor Study. J Clin Oncol 2015;33:2545–52. doi:10.1200/JCO.2014.57.7528.

[101] Kwak M, Zebrack BJ, Meeske KA, Embry L, Aguilar C, Block R, et al. Trajectories of psychological distress in adolescent and young adult patients with cancer: A 1-year longitudinal study. J Clin Oncol 2013;31:2160–6. doi:10.1200/JCO.2012.45.9222.

[102] Bellizzi KM, Smith A, Schmidt S, Keegan THM, Zebrack B, Lynch CF, et al. Positive and negative psychosocial impact of being diagnosed with cancer as an adolescent or young adult. Cancer 2012;118:5155–62. doi:10.1002/cncr.27512.

[103] Carpentier MY, Fortenberry JD, Ott MA, Brames MJ, Einhorn LH. Perceptions of masculinity and self-image in adolescent and young adult testicular cancer survivors: Implications for romantic and sexual relationships. Psychooncology 2011;20:738–45. doi:10.1002/pon.1772.

[104] Wright CI, Coad J, Morgan S, Stark D, Cable M. Just in case: The fertility information needs of teenagers and young adults with cancer. Eur J Cancer Care (Engl) 2014;23:189–98. doi:10.1111/ecc.12137.

[105] LIVESTRONG. LIVESTRONG Fertility Programme n.d. https://www.livestrong.org/what-we-do/program/fertility (accessed January 30, 2018).

[106] Burns KC, Boudreau C, Panepinto JA. Attitudes Regarding Fertility Preservation in Female Adolescent Cancer Patients. J Pediatr Hematol Oncol 2006;28:350–4. doi:10.1097/00043426-200606000-00006.

[107] Saito K, Suzuki K, Iwasaki A, Yumura Y, Kubota Y. Sperm cryopreservation before cancer chemotherapy helps in the emotional battle against cancer. Cancer 2005;104:521–4. doi:10.1002/cncr.21185.

[108] Valle CG, Tate DF, Mayer DK, Allicock M, Cai J. A randomized trial of a Facebook-based physical activity intervention for young adult cancer survivors. J Cancer Surviv 2013;7:355–68. doi:10.1007/s11764-013-0279-5.

[109] Rabin C, Simpson N, Morrow K, Pinto B. Intervention format and delivery preferences among young adult cancer survivors. Int J Behav Med 2013;20:304–10. doi:10.1007/s12529-012-9227-4.

[110] Richards M, Corner J, Maher J. The National Cancer Survivorship Initiative: New and emerging evidence on the ongoing needs of cancer survivors. Br J Cancer 2011;105:S1–4. doi:10.1038/bjc.2011.416.

[111] Hawkins M. Teenage and Young Adult Cancer Survivor Study (TYACSS). n.d. https://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/CCCSS/TYACSS/index.aspx (accessed January 24, 2018).

[112] Lindner O, Stark D. (Abstract) SHARED COMMUNITY FOLLOW-UP SERVICE: A NEW MODEL OF CARE FOR GERM CELL TUMOUR PATIENTS. A PROOF-OF-CONCEPT STUDY. Teenagers Young Adults with Cancer Bright. Conf., Leeds: 2017.

[113] Alliance JL. Teenage and Young Adult Cancer. The top 10 priorities. n.d. http://www.jla.nihr.ac.uk/priority-setting-partnerships/teenage-and-young-adult-cancer/the-top-10-priorities.htm (accessed January 25, 2018).