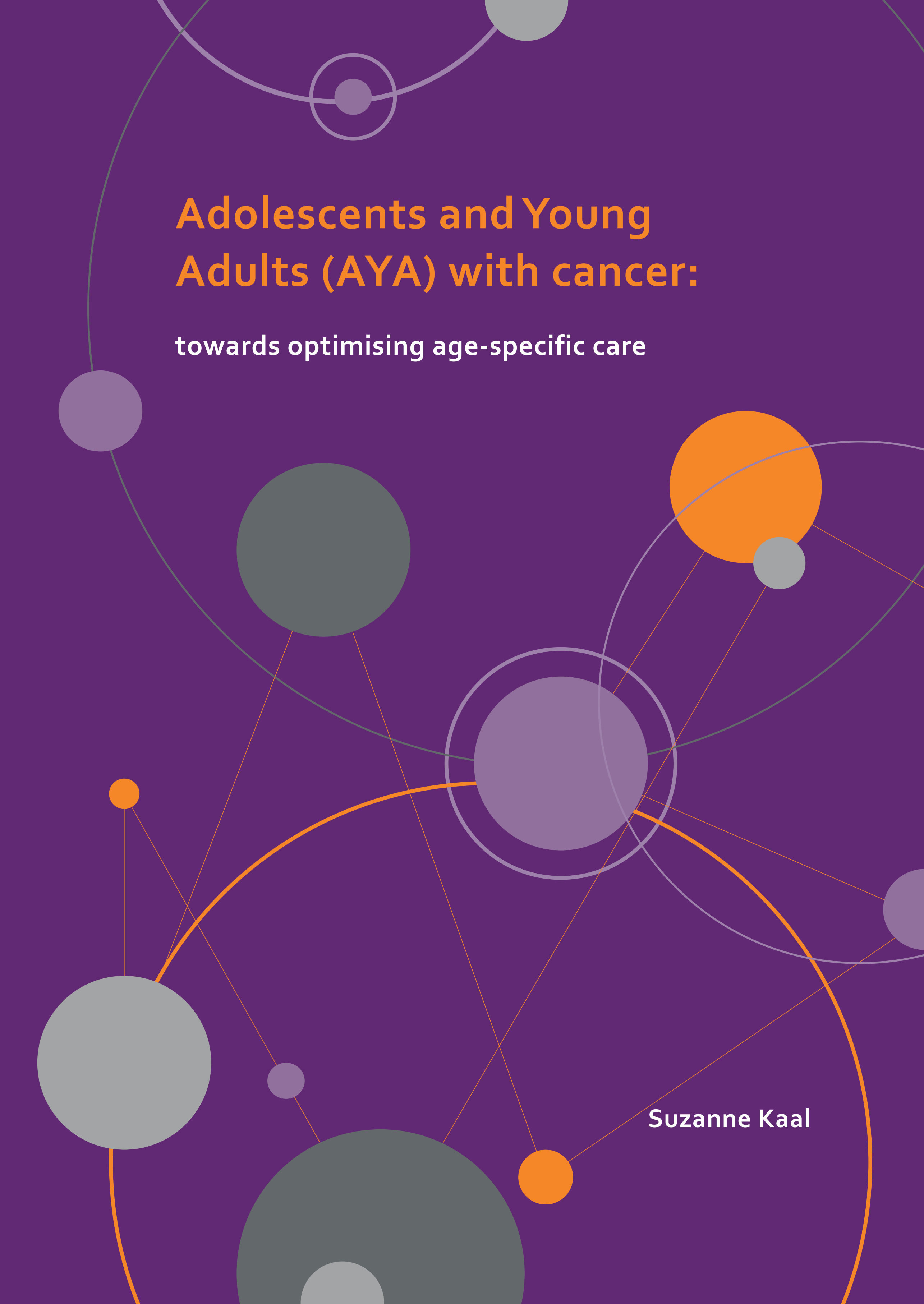
Adolescents and Young Adults (AYA) with cancer:

towards optimising age-specific care



Suzanne Kaal

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Colofon

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Suzanne Elisabeth Jacqueline Kaal

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Promotoren
Prof. dr. W.T.A. van der Graaf
Prof. dr. J.B. Prins

Copromotor
Dr. O. Husson

Manuscriptcommissie
Prof. dr. A.E.M. Speckens
Prof. dr. D.D.M. Braat
Prof. dr. A.J. Gelderblom (LUMC)

Voor mijn ouders

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Chapter 1

General introduction

Adolescents and young adults: defining the age group

Over the past decades there is growing attention for adolescents and young adults (AYA) diagnosed with cancer[1]. Stuck between paediatric and adult oncology, AYA cancer patients form a distinct, understudied and underserved group in cancer care[2,3,4]. The definition of the AYA age range focussing on young cancer patients has evolved over time. There is international consensus that the definition of adolescence in the context of cancer ranges from 15 to 19 years and that adolescence has a transition to young adulthood, starting in the early twenties[5]. However, there is no agreement on the upper age limit; 24, 25, 29, 35 and 39 years have been used[6]. The US National Cancer Institute defines AYA age as 15-39 years at cancer diagnosis, but also proposed that the age range should be handled with flexibility, depending on the research question and the health care system[4,7]. Conceptually, definitions can be based on physical and psychological development and the accompanying care system (paediatric versus adult oncology), aspects of tumour pathology or biology, or on health outcomes[8,9]. In the Netherlands, the definition of the AYA age range ,18-35 years at cancer diagnosis, is based on the organisation of the health care system, in which there is a clear distinction between paediatric (birth to 18 years) versus adult oncology (18 years and older). The upper age limit of 35 years was chosen based on cancer epidemiology. Over the age of 30 there is an increasing number of patients with common cancers, in particular breast cancer, for which already dedicated cancer care teams exist, which is increasingly the case beyond the age of 35 years. Furthermore, to start a new dedicated AYA service, the numbers should be such that it is worthwhile to instigate age-specific services, as AYA patients - in contrast to paediatric cancer patients - are dispersed among several hospitals in the Netherlands. This means that the upper age limit should not be too low. Therefore, the pragmatic Dutch AYA age definition is 18-35 years at diagnosis.

The AYA cancer patient: what makes them a unique group in oncology?

Epidemiology

Cancer at AYA age is rare. In the Netherlands approximately 2,700 AYA patients, aged 18- 35 years, are diagnosed with cancer annually - around five times the number of cases diagnosed in children aged 0-17 years[10]. The incidence of cancer is rising, specifically among those aged 25-39 years and for melanoma, testicular, thyroid, breast and colorectal cancers. AYAs typically present with either a paediatric malignancy at older age (e.g. acute lymphoblastic leukaemia (ALL), brain tumours), a tumour typically of AYA age (e.g. Hodgkin's disease, germ cell tumour, melanoma or thyroid cancer) or with an adult carcinoma at relatively young age (e.g. breast and colorectal cancer)[11]. Lymphomas, breast, melanoma, testicular, colorectal and thyroid cancer, female genital tract malignancies, bone and soft tissue sarcomas, leukaemias and central nervous system cancers account for 95% of the cancers in this age group. The frequency and incidence of distribution of cancer types is remarkably different across the age spectrum of AYA patients, with -as stated above- more and more carcinomas being diagnosed among patients in their thirties. Five-year relative survival rates for AYAs with cancer continue to increase in the Netherlands, exceeding 80% for all diseases combined[10]. Although the gains occur for some tumour types more slowly than in children and older adults, a fairly good survival is found for most tumour types, with a marked exception for e.g. certain leukaemias, central nervous system tumours, and some sarcomas (e.g. rhabdomyosarcoma). Potential reasons for the relatively lack of progress in survival for some tumour types are delay in diagnosis due to unfamiliarity with cancer at AYA age[12,13], differences in disease biology (cancers that are histologically indistinguishable across the age spectrum may be characterised by particular adverse biological features in the AYA population (e.g. increasing complexity with age, such as is seen in synovial sarcoma)[14,15], low clinical trial availability and participation rates[16,17], lack of knowledge and paediatric sparring partners in adult teams regarding typical paediatric cancers, possibly relatively poorer tolerance of chemotherapy schedules in AYA as compared to children[7,18-20].

Developmental phase

Adolescence and young adulthood are complex phases of life due to the many rapidly occurring developmental, emotional and social transitions. Young people aim to achieve many developmental milestones in a rather short time frame such as completing education, establishing autonomy, creating their own identity, forming (romantic) relationships, pursuing gainful employment, becoming financially independent and starting a family[21,22]. The period of adolescence and young adulthood, characterised by physical growth on the one hand and psychosocial maturation on the other hand, has three developmental stages. Each developmental phase is characterised by different dilemmas. In early adolescence (12-18 years) group identity is an important milestone. Adolescents find safety and trust in peer groups based on mutual characteristics, which helps them to become more detached from their parents. In adolescents with severe illness, there is a risk that this milestone will not be reached, due to absence at school where groups usually are formed. This can lead to feelings of alienation and problems with forming social networks. The period of late adolescence (19-22 years) comes with forming personal identity and roles. Severe and chronic illness may hinder a person to develop an own identity and the dominant patient role may interfere with the achievement of personal, social or educational plans. This can result in adjustment problems and diminished self-esteem. In young adulthood (23-34 years) partner relationships and intimacy are important milestones. Young people who do not achieve these milestones in early adulthood may experience isolation[23,4]. In all three developmental phases experimenting with these transitions and dilemmas is very important, however still with the support and within the safety net of family and peers.

Cancer challenges AYAs' abilities to achieve these milestones, which can lead to stagnation of their normal development[24]. Although AYA cancer patients experience challenges similar to those of older and younger patients, including short-term (e.g. hair loss, nausea) and long-term effects of cancer treatment (e.g. pain, psychological distress, fear of cancer recurrence), these effects interfere more severely with daily functioning in combination to age-specific challenges of specific developmental phases. Cancer often forces AYAs to move back home and become dependent on parents, usually after periods of time living independently or while just discovering and experiencing newfound autonomy and independence. Changes in physical appearance resulting from treatment (e.g. amputation, hair loss or weight change) can negatively impact body image (looking not similar to peers) and interfere with self-esteem and identity development. Negative body image, low self-esteem, infertility concerns, or feeling abnormal due to cancer and its treatment might negatively influence AYAs' readiness and ability to engage in romantic relationships or sexual activities. Often, AYAs have concerns about sexuality and procreation, which are not always expressed by themselves or addressed by their treating physicians and some AYA experience a delay in achieving psychosexual milestones (e.g. dating and sexual intercourse), while others may show sexual risky behaviour[25]. In young adults, emotional and financial burden of a cancer diagnosis may have negative impact on the partner relationship leading to distress among AYAs and their partners. Isolation and alienation are commonly reported among AYAs with cancer, particularly when they miss part of the peer group life because of cancer treatments and, therefore, lack experiences being shared by their healthy peers. AYAs frequently report difficulties maintaining or making new relationships as they feel anxious about fitting into their peer group again. On top of these emotional roller coasters, cancer treatment and long-term and late medical effects can lead to serious disruption in education and lead to employment problems (unemployment, returning back to work, job insecurity) which may give AYAs the feeling of being "left behind". In addition, AYA cancer survivors report issues with getting mortgages and insurances, and have to deal with financial difficulties. Young adults with young families are faced with competing responsibilities in which care for children and lack of transportation for hospital visits, may also lead to lower treatment compliance levels[21]. These AYA age-specific topics are nicely shown in figure 1.

Figure 1: Age-specific topics in the AYA cancer patient population

Part I: Health-related quality of life, psychosocial outcomes and adaptations

For decades, the success of cancer treatments has focused on objective outcomes such as radiological response, progression-free and overall survival, and healthcare-provider perspective of treatment-related toxicities. More recently, increasing attention has been given to patient reported outcomes (PROs), defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'[26], in order to evaluate treatment efficacy. PROs include a range of outcomes such as symptoms, functioning and health-related quality of life (HRQoL). HRQoL is the most widely used PRO and is defined as a multidimensional concept that includes the patient's perception of the impact of the disease and its treatment on physical, psychological and social functioning. Data on HRQoL in AYA patients are still limited, however, as described above, many patients experience a substantial burden of physical and psychological symptoms, with an adverse impact on HRQoL. Two recent review papers showed that AYA with cancer experience worse HRQoL compared with a normative population[27,28]. HRQoL assessment in clinical practice throughout the course of the disease is important as it can facilitate communication, improve symptom control and patient satisfaction and reduce hospital admissions[29].

Negative and positive outcomes

Within the perspective of the developmental phases, the emergence of distress or resilience is a function of the extent to which the illness interrupts key developmental tasks, and/or the extent to which the young person is able to mitigate these hurdles to normal, age-appropriate development[30].

Negative outcomes associated with cancer at AYA age

In order to provide optimal age-specific supportive care it is important to get insight into the prevalence of AYA (age-specific) HRQoL issues and identify AYA patient subgroups that might be more susceptible to poor HRQoL outcomes and subsequently might benefit from additional support or interventions. Apart from patients' point of view it is essential that health care professionals are aware of which HRQoL issues matter most to AYA cancer patients. Because cancer at AYA age is rare, many health care professionals only occasionally have to care for AYA patients and therefore may have a lack in their knowledge and unintentionally deliver less optimal age-specific care. Two important issues AYA cancer patients may be confronted with are fear of cancer recurrence and fatigue[7]; both may have debilitating effects on their HRQoL. Fear of cancer recurrence is defined as the "fear, worry, or concern relating to the possibility that cancer will come back or progress"[31]. Previous research showed that psychosocial help for fear of cancer recurrence is a key unmet need among AYA[2]. However, less is known about the prevalence and correlates of fear of cancer recurrence among AYA. Cancer-related fatigue is one of the most common and distressing symptoms reported by cancer patients in general both during and after cancer treatment[32,33]. Little is known about the prevalence, impact, and correlates of severe fatigue among AYAs.

Positive outcomes associated with cancer at AYA age

Next to a negative impact, AYA cancer patients may also experience positive (adaptive) outcomes, like post-traumatic growth and resilience. Post-traumatic growth is described as the positive psychological change that appears following significantly burdensome or traumatic life events[34]. Resilience is the ability to cope with negative emotions that arise from a stressful experience, by identifying and developing resources to function[35]. Over the past decade psychosocial research in AYA has broadened its scope from negative to positive aftermath of cancer. It could be hypothesized that both post-traumatic growth and resilience might promote HRQoL and buffer negative consequences of cancer. Empowerment is also a positive factor that may be associated with HRQoL and has been introduced as issue in cancer survivorship research over recent years[36-39]. Empowerment is the feeling of being able to manage the challenge of the cancer experience and having a sense of control over one's life[40]. Empowered AYA cancer patients may be more likely to understand and participate in their own care by mobilizing resources and taking actions that can reduce distress, enhance strategies for dealing with cancer and improve HRQoL[36,37]. It is therefore important to evaluate which sociodemographic, clinical and psychological factors are associated with positive outcomes among AYA cancer patients.

Part II: Supportive and palliative care

AYA cancer patients have often been identified as the "lost tribe". There is no medical "home" for AYAs with cancer as neither paediatric departments, which are disease and family-focused, nor adult oncology departments which are mainly disease-focused, are able to provide age-adjusted care to this specific group[9]. This is even more the case for AYA cancer patients who are in a palliative trajectory. They may lack the option of family care and may feel too young for general palliative and hospice care. It is, therefore, of great importance to understand the needs of the AYA cancer patients in different stages of cancer.

Psychosocial and supportive care needs

The psychosocial and supportive care needs of AYAs tend to be broader in scope and intensity compared to younger and older patients, because of the many developmental, emotional and social changes and transitions that occur in a rather short period of time during this specific phase of life. Data from a large national survey of 523 AYA cancer survivors in the USA found that 53%

of them reported having six or more unmet information needs (e.g. developing another type of cancer, signs of cancer recurrence, late effects of cancer, family members' risk of cancer, financial needs, and fertility issues). Furthermore, 35% had unmet service needs, especially with regard to peer support and psychosocial supportive care[2]. Another national survey among 1395 AYA cancer survivors in the USA has shown that the most commonly reported unmet needs were addressing recurrence concerns (80%), followed by information on late effects (78%), family risk of cancer (51%), and fertility information (45%)[41]. Having unmet information or service needs was associated with poorer HRQoL[42,43].

Palliative and end-of-life care

The World Health Organization defines palliative care as "an approach that improves the HRQoL of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other physical, psychosocial and spiritual problems"[44]. Palliative care in AYA cancer patients is different since AYA have had less time to learn from other adverse life experiences to help manage the effects of advanced disease. They face many complicated decisions but may lack the fully developed executive functioning and abstract thinking necessary for medical decision-making and coping with uncertainty[45]. AYAs can report anticipatory grief over their lives that have not yet been lived and they incline to act normal as long as possible. A previous study showed that AYAs who die in the hospital tend to use palliative care services very late in the course of the disease and often undergo aggressive treatment until death is near[46]. A timely introduction of palliative care would have great use in providing physical, psychosocial, and spiritual support. Palliative care should be part of the comprehensive cancer care for AYAs[47]. It is important not to assume that AYA patients may be less willing to discuss death and other end-of-life issues like nutrition/hydration, sedation, treatment cessation and place of death[48]. Another important aspect of palliative and end-of-life care concerns the interprofessional communication. Optimal and timely communication between hospital health care professionals and general practitioners is essential for a good transition of care. Although this statement can be made for all patients who don't need any further hospital-based care, the specific needs and issues that play a role in end stage life of AYA cancer patients should be addressed properly. Moreover, end-of-life care for AYA cancer patients differs from 'normal' adult end-of-life care since AYA do not frequently have comorbidities and can therefore have a longer process of dying.

Organisation of care for AYA cancer patients in the Netherlands: the Dutch AYA 'Young and Cancer' Platform

Over the last decades, the oncology community became aware of the gap in the care needs and outcomes of AYA cancer patients[1,4]. Comprehensive assessment of the needs is necessary to optimise services for AYAs. The existing organisational models of paediatric and adult (medical) oncology are not ideally suited to the complex needs of AYA patients, which require a different, new, patient-focused multidisciplinary approach[1]. National AYA programs were formed in an attempt to bridge the gap between the two worlds and address unmet care needs of this patient group. In the Netherlands, in 2009, the Radboud university medical center (Radboudumc) in Nijmegen, in the east of the Netherlands, launched the AYA Expertise Platform, in a close collaboration between AYAs and professionals[49]. The main goal of the Platform was to improve the care for and the quality of life of AYA cancer patients by offering structural, standardised, comprehensive and patient-centered AYA cancer care. An AYA outpatient clinic was launched where AYA cancer patients, regardless of their treatment status, type and intent of treatment, could address their age specific questions to a dedicated multidisciplinary AYA team (nurse, medical oncologist, psychologist and social worker). Interviews with AYAs showed that one of the most important unmet needs was (digital) peer support. Therefore, in 2010 an online community named AYA4 (All Information You've Asked for) was developed by and for AYA cancer patients treated at the Radboudumc. The online community became available for all AYA cancer patients in the Netherlands in 2014.

Aims and content of this thesis

The overall purpose of this thesis is to gain scientific knowledge about the most important HRQoL issues, psychosocial outcomes and adaptations and quality of care issues among Dutch AYA cancer patients, leading to insights into the (further) development of optimal age-specific AYA care. The current thesis can be divided in two parts. Part I addresses HRQoL, psychosocial outcomes and adaptations. Part II describes supportive and palliative care initiatives.

Part I: Health-related quality of life, psychosocial outcomes and adaptations

The first part of this thesis is focused on HRQoL in general and on specific psychological issues AYA cancer patients are confronted with that may affect their HRQoL, in particular fear of cancer recurrence and fatigue. In **Chapter 2** the ten most important HRQoL issues for AYA cancer patients will be investigated and a comparison with the perception of health care professionals will be made to determine whether there is a discrepancy in assessment of disease impact between patients and professionals. In **Chapter 3** the prevalence, correlates of high fear of cancer recurrence and its association with HRQoL in AYA cancer patients who visit the multidisciplinary team of the AYA outpatient clinic will be explored. In **Chapter 4** the prevalence of severe cancer related fatigue in AYA cancer patients will be subject of study and will be compared with matched population-based controls. This chapter will also report on the impact of severe fatigue on HRQoL of AYA cancer patients. In addition, correlates of fatigue severity will be studied.

Next to negative consequences, patients with cancer at AYA age may also experience more positive psychosocial outcomes related to personal resilience or feelings of empowerment and post-traumatic growth. In **Chapter 5** an overview of the literature on post-traumatic growth and resilience in AYA cancer patients will be given to explore the most important clinical, sociodemographic and psychological variables associated with post-traumatic growth and resilience, their relationship with HRQoL and possible interventions to improve PTG and/or resilience. In **Chapter 6** the levels and associated factors (demographic, clinical and psychological) of empowerment and the association between empowerment and HRQoL will be examined in AYA cancer patients.

Part II: Supportive and palliative care

The second part of this thesis is focused on supportive care aspects among AYA cancer patients. In **Chapter 7** a study on the secure online support community for AYA cancer patients will be described by providing user statistics, questionnaire data about usefulness, and a content analysis. As one in five AYA patients eventually die of cancer, the availability of age-adjusted palliative care including end-of-life care is of utmost importance. In **Chapter 8** the experiences of bereaved parents concerning the palliative care for their child and (after) care for themselves, social support and their psychological wellbeing will be investigated. In addition, the experiences of general practitioners regarding the palliative care of a terminally ill AYA cancer patients and their families will be studied. Finally, **Chapter 9** will provide a summary and discuss the practical implications of the findings presented in this thesis and makes recommendations for future research.

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Chapter 2

Health-related quality of life priorities in adolescents and young adults (AYA) with cancer: discrepancies with health care professionals' perceptions

Suzanne EJ Kaal, Judith B Prins, Rosemarie Jansen, Eveliene Manten-Horst, Petra Servaes, Winette TA van der Graaf, Olga Husson

submitted for publication

Abstract

Objectives: To determine health-related quality of life (HRQoL) priorities of adolescent and young adult (AYA) cancer patients and examine discrepancies between AYA and health care professionals (HCP).

Methods: Dutch AYA cancer patients aged 18-35 years at time of cancer diagnosis (N=83) and Dutch HCP (N=34) involved in AYA oncology were invited to complete the Quality of Life for Cancer Survivors questionnaire.

Results: Patients scored significantly lower on negatively formulated HRQoL issues (e.g. fatigue, coping difficulties, feeling isolated) and significantly higher on positive formulated issues (e.g. support from others, overall physical health, happiness) compared to HCP. The most important issues for AYA cancer patients were: perceived support from others, distress about initial cancer diagnosis, distress for family, overall quality of life and happiness. HCP perceived distress about initial cancer diagnosis, distress for family, cancer treatment distress, interference of illness with employment/study and fatigue as most important for AYA. The top 10 priorities of patients vs. perceptions of HCP overlapped for 5 of 10 issues.

Conclusion: AYA cancer patients perceived most HRQoL items as less problematic compared to HCP. The discrepancy between patients and HCP illustrates the importance of patient participation, i.e. involving patients in organizing and prioritizing their own (psychosocial) care.

Introduction

Adolescents and young adults (AYA), being diagnosed with cancer at the age of 18 to 35 years, are a distinct group halfway between paediatric and adult oncology. Over the last decades, the incidence of cancer in AYA has increased in Europe as well as the United States and Canada [1-3]. In the Netherlands about 2700 new patients per year are diagnosed with cancer in this age group [4]. Although the improvement in survival rates of AYA cancers lags behind that of childhood and adult cancers, the vast majority of AYA cancer patients will become survivors as the overall 5-year survival rate in the Netherlands is 80% [5].

AYA cancer patients are in a phase of life where they have to reach developmental milestones such as completing education, getting intimate relationships, pursuing gainful employment or having children [6]. Cancer challenges AYAs' abilities to achieve these milestones. Problems concerning self-esteem, autonomy, body image, fertility and sexuality may have a negative impact on health-related quality of life (HRQoL) of AYA cancer patients [6-8].

In recent years there is increasing attention to patient-reported outcomes (PROs), including HRQoL assessment in AYA cancer patients [9]. A PRO is defined as information about the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [10]. Patients' HRQoL can be evaluated in multiple domains including physical, psychological, social, and spiritual well-being [11,12]. HRQoL measurement in AYA cancer patients allows physicians to better understand the complexity of taking care of AYAs with cancer [9,13-15]. Validated HRQoL questionnaires are mostly analyzed on scale level and although this is psychometrically the soundest method, it can cause loss of information. Evaluating HRQoL on item level will provide more detailed information about which items result in low scale scores and about aspects of HRQoL where AYA patients need more (age-specific) support.

To achieve optimal patient-centred care, it is essential that health care professionals (HCP) are able to assess AYAs' needs and preferences. A previous study in Australia showed that most oncology professionals recognized the unique nature of the AYA population (defined as cancer patient 15-25 years) regarding biological, genetic, epidemiological, psychological, social and cultural factors. In that study the results of the HCP were compared with previous research on unmet needs among AYA cancer patients. HCP broadly misrepresented the priorities of AYA as being related to survival outcomes, concerns about death and dying, and functional well-being. HCP perceptions were largely in contrast with the priorities of AYA following a cancer diagnosis, which related more broadly to issues associated with normal life stage development including peer and family relationships, engagement in education and employment, development of autonomy and treatment environment (in- or outpatient, facilities, staff) [16]. Although this Australian study showed significant discrepancies for the younger AYA patients with cancer compared to HCP, it is not clear if the discrepancies also exist for young adults diagnosed with cancer between 18 and 35 years. One could assume that this age group has reached another life phase with different milestones, more responsibilities and more independence from parents in comparison to cancer patients aged 15-25 years. Moreover, it would be interesting to evaluate whether this incongruence exists in the Dutch system with its clear distinction between paediatric and adult oncology.

Assessing HRQoL priorities and providing care according to these priorities might lead to higher patient satisfaction and can improve doctor-patient partnership and ultimately overall quality of care [17]. Therefore, the aims of the current study are to: 1) determine the top ten HRQoL priorities on item level relevant to AYA cancer patients (according to gender, cancer type, treatment intention, partner status and having children); 2) determine whether there is a discrepancy between items prioritized by AYA patients and oncology HCP.

Methods

Participants

Patients aged 18 to 35 years at time of cancer diagnosis and who had been seen by at least one of the members of the AYA team of the Radboud university medical center (Radboudumc) in The Netherlands, were invited to participate in this study. The Radboudumc is an expert center in delivering age-specific care for AYA cancer patients during and after cancer treatment. The AYA team is a dedicated multidisciplinary team including a medical oncologist, clinical nurse specialist, medical psychologist, and social worker. Patients consulting the AYA team receive standard medical care from their own treating physician in the Radboudumc (medical oncologist, haematologist, surgeon, gynaecologist etc.) and visit the AYA team for age-specific questions and care needs. In general, patients visiting the AYA team represent a group of patients with high disease severity, diagnosed with relatively advanced stage of disease and undergoing intensive treatments, and reporting more difficulties with coping. Patients with lower stage disease treated solely by surgery, are not often seen by the AYA team. For this study, AYA patients were included independently of the status of treatment (during or after treatment), the type of treatment (surgery, chemotherapy, radiotherapy, immunotherapy/targeted therapy and hormonal therapy or a combination), or the number of AYA team visits (some patients only had one introduction talk with one of the members of the team and did not receive specific care thereafter, whilst others visited members of the AYA team more frequently) to depict the real-life heterogeneous sample of AYA cancer patients visiting the AYA team. Inclusion commenced January 2012 and ended March 2016.

Dutch HCP involved in AYA oncology were asked at the 2017 annual AYA congress on age-specific care to participate in the study. Moreover, an e-mail was sent to the HCP members of the Dutch AYA 'Young and Cancer' Platform in order to ensure maximal participation rate. Background information of the HCP was gathered including age, gender, type of oncology HCP, hospital name and how many AYA cancer patients they saw per month via self-developed questions. HCP were asked to complete the Quality of Life for Cancer Survivors questionnaire according to their thoughts of the items that play a role in the AYA population after being treated for cancer.

Procedure

Potential study participants were recruited via letters describing the study and inviting patients to participate. Patients who were willing to participate had to actively opt-in to the study by providing written informed consent by e-mail to a member of the AYA team. Participants were then sent the questionnaire by e-mail that could be completed online. The study was deemed exempt from full review and approval by a research ethics committee (CMO Regio Arnhem-Nijmegen, #2016-2872)

Measures

Sociodemographic and clinical characteristics

Demographic data, including age, sex, partnership, having children, living situation, educational level and employment status were gathered by self-report. Medical data, including tumour type, disease stage, type(s) of treatment(s) received, treatment status at participation (on/off treatment) and time since initial diagnosis were extracted from the patients' medical records by one of the researchers (SK).

Health-related Quality of Life Questionnaire

AYA cancer patients

The Quality of Life for Cancer Survivors (QoL-CS) questionnaire measures the HRQoL of cancer patients. It consists of 41 items on the physical, mental, social, spiritual impact of cancer on the life of the patient. Respondents rate themselves along an interval rating scale ranging from 0 to 10 for each item. An overall QoL score was computed by averaging all 41 items [18]. We adapted the questionnaire slightly by adding four items (neuropathy = a burning or tingling sensation or a feeling of numbness, concerns of dying, concerns about fertility, concerns that family members will get cancer). These reflect problems/concerns faced in daily clinical practice. The items local recurrence and distant metastases have been combined into 1 item. Therefore, the total number of items is 44. Questions can be negatively or positively formulated. A negatively formulated question means that a higher score illustrates a bigger problem, for example: 'To what extent is sleeping a problem?' (0=no problem, 10= very big problem). A positively formulated question means that a higher score illustrates more benefit, for example: 'How useful do you feel?' (0=not at all, 10= very useful).

Statistical analysis

Analyses were performed using SPSS statistical software (version 24, Chicago, IL, USA) and two-sided *p* values of <.05 were considered statistically significant. Differences in HRQoL items between two groups were compared with an independent t-test and between more than two groups with an analysis of variance (ANOVA). For AYA cancer patients HRQoL items were analysed according to five variables: gender (male/female), cancer type (testicular, sarcoma, breast, haematologic, gynaecologic and other), treatment intention (curative/palliative), partner (yes/no) and children (yes/no). Three items (importance of religious activities, importance of spiritual activities and spiritual change) were excluded, as they reflect religious aspects and their intrinsic value differs per person dependent on cultural and religious background. Clinical significance was determined by applying Normans rule of thumb (observed difference exceeds 0.5 x mean standard deviation)[19].

Results

Sociodemographic and clinical patient characteristics

In total, 309 letters requesting participation in the study were sent to AYA cancer patients visiting one of the members of the AYA team. A total of 89 patients, comprising 57% of those who opted to take part in the study (155 patients) and 29% of those invited (309 patients) completed the online questionnaire. The remainder 66 patients eventually did not fill out the questionnaires after they previously agreed to do this. A small part of non-participation was due to technical problems when returning the online questionnaires. Six patients were excluded due to age criteria: 4 were diagnosed with cancer <18 years and 2 were aged >35 years at the time of diagnosis. Table 1 displays sociodemographic, disease, and treatment-related characteristics of the final sample (83 patients). The mean age at the time of diagnosis was 27.5 (SD=4.6) years with a range of 18 to 35 years and a median age at diagnosis of 27 years. The average time since diagnosis was 2.1 years (SD=2.6) and 86% of patients received curative treatment. Of the participants, 52% were male. The most commonly diagnosed cancers were testicular cancer (34%) and sarcoma (19%).

Characteristics health care professionals

Thirty-four HCP derived from 12 hospitals, filled out the QoL-CS questionnaire. Among them were 11 medical oncologists, 5 nurse specialists, 11 nurses, 1 social worker, 1 physical therapist, 1 rehabilitation specialist, 2 psychologists and 1 who did not report his/her medical profession. Their mean age was 45 years with a range of 23 to 64 years. Of the HCP 12% (n=4) were male. Each of them guided a mean of 15 (range 1-70) AYA cancer patients monthly. Four HCP were from non-university hospitals.

HRQoL items

Table 2 shows mean (+SD) scores on HRQoL items for AYA cancer patients and HCP. HCP rated physical symptoms like fatigue, appetite, pain, constipation, sleep disorders, nausea and neuropathy among AYA cancer patients significantly higher compared to what AYA cancer patients reported as their own most relevant issues. These differences were clinically relevant. AYA cancer patients rated overall physical health and quality of life, happiness, satisfaction, usefulness and support from others (all positively formulated questions) significantly higher compared to HCP. HCP rated distress about time since treatment completion, anxiety, depression, fear of future tests, fear of recurrent cancer, fear of dying, problems with personal relationships, sexuality, concerns about fertility, interference with illness of employment/study, feeling isolated, uncertainty about the future and life purpose as clinically relevant and more important HRQoL items in comparison to AYA cancer patients.

Table 1: Demographic and clinical data of AYA cancer patients

	AYA cancer patients N=83
Gender	
Male	43 (52%)
Female	40 (48%)
Age at diagnosis, mean	27.5 (4.6)
Age at survey	29.6 (4.8)
Time since cancer diagnosis	2.1 (2.6)
Cancer diagnosis	
Testicular cancer	28 (34%)
Sarcoma	16 (19%)
Breast cancer	10 (12%)
Lymphoma/leukaemia	10 (12%)
Gynaecological cancer	9 (11%)
Melanoma	3 (4%)
Other *	7 (8%)
Stage	
NA	9 (11%)
Stage 1	11 (13%)
Stage 2	25 (30%)
Stage 3	13 (16%)
Stage 4	18 (22%)
Unknown	7 (8%)
Treatment intention	
Curative	71 (86%)
Palliative	12 (14%)
Treatment status at participation	
Active	22 (27%)
Completed	61 (73%)
Treatment type	
Surgery	70 (84%)
Chemotherapy	72 (87%)
Radiotherapy	24 (29%)
Immunotherapy/targeted therapy	13 (16%)
Hormonal therapy	7 (8%)
Systemic therapy other	13 (16%)
Partner	
Yes	58 (70%)
No	24 (29%)
Children	
Yes	27 (33%)
No	55 (66%)

Table 1: Continued

Living situation	
With parents	14 (17%)
On own	24 (29%)
With partner	44 (53%)
Highest completed education	
Low/intermediate vocational education or less	38 (46%)
High-level vocational education and/or university	44 (53%)
Employed/studying	
Yes	68 (82%)
No	15 (18%)

Not all numbers add up to 83 because of missing data
*Other cancer types comprise brain tumour (n=1), sigmoid carcinoma (n=1), oropharyngeal cancer (n=1), neuroendocrine tumor (n=1), salivary gland cancer (n=1), adrenal carcinoma (n=1), lung cancer (n=1)

Table 3a shows the top ten of most relevant HRQoL items rated by AYA cancer patients and HCP and the overlapping items in the middle column. Support from others was ranked as the most important HRQoL item among AYA cancer patients, followed by distress about initial cancer diagnosis and distress for family. These last two items were ranked as most important by HCP. Only five out of ten items were similar for patients and HCP. Six out of ten items of AYA cancer patients were positively formulated. Table 3b displays top ten HRQoL items rated by AYA cancer patients and HCP for only negatively formulated items. It shows that the first three items are similar for both groups (distress about cancer diagnosis, distress for family and distress about cancer treatment). Six out of ten items overlapped.

Table 4 depicts the top ten most important HRQoL items for AYA cancer patients according to gender, cancer type, treatment intention, partner and having children. It shows that male AYA cancer patients scored significantly higher on items concerning quality of life, happiness, satisfaction, hopefulness, overall physical health and experienced less interference with activities at home. The difference between males and females on the item satisfaction was not clinically relevant. Between tumour types there were differences on the items: quality of life, happiness, cancer treatment distress, overall physical health and interference with activities at home. For sarcoma patients these effects were more outspoken than for patients with other cancer types. AYA cancer patients treated with curative intention scored significantly higher on items concerning quality of life, hopefulness and overall physical health in comparison

Table 2: Mean scores (SD) on HRQoL items of AYA cancer patients and health care professionals

	AYA (n=83)	Health care professionals (n = 34)	P-value
Physical well-being			
Fatigue	4.4 (2.7)	7.3 (1.2)	0.000**[a]
Appetite	1.5 (2.2)	5.1 (2.3)	0.000**[a]
Pain	2.3 (2.3)	4.3 (2.0)	0.000**[a]
Constipation	1.8 (2.4)	3.7 (1.8)	0.000**[a]
Sleep	2.8 (2.8)	5.2 (1.9)	0.000**[a]
Nausea	1.6 (2.6)	4.8 (2.3)	0.000**[a]
Menstrual changes	3.7 (3.8)	5.2 (2.5)	0.074
Neuropathy	2.2 (2.5)	4.8 (2.6)	0.000**[a]
Overall physical health [b]	6.6 (1.6)	5.7 (1.4)	0.004**[a]
Psychological well-being			
Coping difficulties	4.1 (2.6)	6.2 (1.5)	0.000**[a]
Quality of life [b]	7.2 (1.7)	6.2 (1.1)	0.003**[a]
Happiness [b]	7.1 (1.9)	6.2 (1.3)	0.012*[a]
Control [b]	5.5 (2.6)	5.1 (1.6)	0.411
Satisfaction [b]	6.8 (1.9)	5.9 (1.3)	0.012*[a]
Concentration/memory [b]	5.7 (2.2)	5.0 (1.6)	0.095
Usefulness [b]	6.4 (2.3)	5.3 (1.6)	0.014*
Appearance	5.0 (3.0)	6.2 (2.0)	0.030*
Self-concept	3.8 (2.8)	6.4 (1.7)	0.000
Distress about initial diagnosis	7.6 (2.5)	8.5 (1.5)	0.054
Cancer treatment distress	6.9 (2.3)	7.8 (1.5)	0.047*
Distress about time since treatment completion	5.5 (2.8)	6.9 (1.4)	0.014*[a]
Anxiety	3.7 (2.7)	6.5 (1.3)	0.000**[a]
Depression	3.0 (2.6)	5.0 (1.3)	0.000**[a]
Fear of future tests	4.7 (2.7)	6.9 (1.4)	0.000**[a]
Fear of second cancer	4.8 (2.9)	5.7 (2.1)	0.107
Fear recurrent cancer	5.4 (2.5)	7.1 (1.2)	0.001**[a]
Fear of dying	4.1 (3.2)	6.2 (1.8)	0.001**[a]
Social well-being			
Family distress	7.6 (2.0)	7.8 (1.1)	0.671
Support from others [b]	8.1 (1.8)	6.2 (1.6)	0.000**[a]
Personal relationships	3.7 (2.9)	6.6 (1.6)	0.000**[a]
Sexuality	4.3 (3.3)	7.2 (1.2)	0.000**[a]
Concerns about fertility	5.0 (3.6)	7.3 (1.8)	0.001**[a]
Interference of illness with employment or study	6.2 (3.0)	7.8 (1.2)	0.004**[a]
Home activities	6.5 (2.7)	7.2 (1.2)	0.105
Feel isolated	3.7 (3.0)	6.1 (1.5)	0.000**[a]
Financial burden	6.3 (3.0)	5.9 (1.6)	0.533
Concerns that family members will get cancer	3.9 (2.8)	4.8 (1.7)	0.097

Table 2: Continued

Spiritual well-being			
Importance of religious activities [c]	2.1 (3.3)	3.6 (1.9)	0.020*[a]
Importance of spiritual activities [c]	1.3 (2.2)	4.4 (2.0)	0.000**[a]
Spiritual change [c]	1.8 (2.4)	4.9 (1.8)	0.000**[a]
Uncertainty future	5.2 (2.9)	6.6 (1.6)	0.010*[a]
Illness positively changed life [b]	5.1 (2.8)	6.2 (1.6)	0.028*
Life purpose [b]	4.5 (3.1)	6.1 (1.6)	0.005**[a]
Hopefulness [b]	6.8 (2.2)	7.3 (1.2)	0.169

*$p<0.05$; **$p<0.01$

[a] = clinical relevant

[b]= Positively formulated item

All other items are negatively formulated: the higher the score, the bigger the problem

[c]= neutral formulated items because of religious background, not in analysis

Table 3a: Top 10 most important HRQoL issues among AYA cancer patients and health care professionals **including** positive formulated items

Rank	AYA cancer patients	Overlap with HCP	HCP	Rank
1	***Support from others (M= 8.1)[a]***	No	Distress initial cancer diagnosis (M = 8.5)	1
2	Distress initial cancer diagnosis (M=7.6)	Yes, with rank 1	Distress family (M = 7.8)	2
3	Distress family (M=7.6)	Yes, with rank 2	Cancer treatment distress (M = 7.8)	3
4	***Quality of Life (M=7.2)[a]***	No	***Interference of illness with employment or study (M = 7.8)***	4
5	***Happiness (M=7.1)[a]***	No	***Fatigue (M = 7.3)***	5
6	Cancer treatment distress (M= 6.9)	Yes, with rank 3	Hopefulness (M = 7.3)[a]	6
7	***Satisfaction (M= 6.8)[a]***	No	***Concerns about fertility (M= 7.3)***	7
8	Hopefulness (M =6.8)[a]	Yes, with rank 6	***Sexuality (M = 7.2)***	8
9	***Overall physical health (M = 6.6)[a]***	No	Home activities (M = 7.2)	9
10	Home activities (M = 6.5)	Yes, with rank 9	***Fear recurrent cancer (M = 7.1)***	10

Unique items for AYA cancer patients or HCP are in ***bold and italics***

[a] = positively formulated questions

M = mean

AYA= adolescent and young adult

HCP= health care professional

Table 3b: Top 10 most important HRQoL issues among AYA cancer patients and health care professionals **excluding** positive formulated items

Rank	AYA cancer patients	Overlap with HCP	HCP	Rank
1	Distress initial cancer diagnosis (M=7.6)	Yes, with rank 1	Distress initial cancer diagnosis (M = 8.5)	1
2	Distress family (M=7.6)	Yes, with rank 2	Distress family (M = 7.8)	2
3	Cancer treatment distress (M= 6.9)	Yes, with rank 3	Cancer treatment distress (M = 7.8)	3
4	Home activities (M = 6.5)	Yes, with rank 8	Interference of illness with employment or study (M = 7.8)	4
5	***Usefulness (M = 6.4)***	No	***Fatigue (M = 7.3)***	5
6	***Financial burden (M = 6.3)***	No	***Concerns about fertility (M= 7.3)***	6
7	Interference of illness with employment or study (M = 6.2)	Yes, with rank 4	***Sexuality (M = 7.2)***	7
8	***Concentration/memory (M = 5.7)***	No	Home activities (M = 7.2)	8
9	***Control (M = 5.5)***	No	***Fear recurrent cancer (M = 7.1)***	9
10	Distress about time since treatment completion (M = 5.5)	Yes, with rank 10	Distress about time since treatment completion (M = 6.9)	10

Unique items for AYA cancer patients or for HCP are in ***bold and italics***
M= mean
AYA= adolescent and young adult
HCP= health care professional

with patients treated with palliative intent. AYA patients with a partner scored significantly higher on happiness, satisfaction and overall physical health. The difference in overall physical health between groups was not clinically relevant. There were no differences in top ten item scores when stratified for having children or not.

Discussion

The results of the current study indicate that there is a considerable discrepancy in top ten HRQoL items prioritized by AYA cancer patients and HCP. About half of HRQoL items rated as important, were similar for patients and HCP. AYA cancer patients rated most HRQoL items as less important than HCP, indicating that professionals believe that the burden of cancer and treatment is larger than is actually perceived by the patients themselves. This holds for all four domains (physical, psychological, social and spiritual) of the QoL-CS questionnaire. Top ten items for AYA cancer patients are dominated by six positively formulated questions, indicating that AYA cancer patients are more inclined to emphasize HRQoL items with a positive connotation like happiness, satisfaction, hopefulness and social support. This phenomenon, expressing

Table 4: Most important HRQoL items (mean(SD)) among AYA cancer patients (n=83) for gender and cancer type

	Gender			Cancer type						
	Male	**Female**	**P-value**	**Testicular**	**Sarcoma**	**Breast**	**Hematologic**	**Gynaecologic**	**Other**	**P-value**
Support from others	8.4(1.6)	7.8 (1.9)	0.082	8.6(1.6)	8.1(1.7)	7.2(1.9)	8.1(2.7)	7.5(1.3)	8.1(1.5)	0.351
Distress initial cancer diagnosis	7.4(2.3)	7.7(2.6)	0.635	7.5(2.2)	6.9(2.6)	7.7(3.3)	6.1(3.0)	8.1(1.7)	8.7(1.9)	0.148
Distress for family	7.7(1.9)	7.5(2.1)	0.620	7.5(1.8)	8.4(1.5)	7.0(2.9)	6.7(2.5)	7.3(2.0)	8.5(1.3)	0.153
Quality of life	7.6(1.5)	6.7(1.8)	0.019*^{a}	8.0(1.4)	6.8(1.8)	7.2(1.0)	7.2(1.2)	6.3(2.3)	6.4(2.1)	0.023* ^{b,c,d,e,f,g,}
Happiness	7.6(1.6)	6.5(2.0)	0,004**^{a}	7.8(1.8)	7.2(1.4)	7.4(1.4)	7.3(1.3)	5.9(2.2)	5.9(2.2)	0.012* ^{c,d,e,f,g,h,i,j}
Cancer Treatment distress	6.7(2.0)	7.1(2.6)	0.428	6.6(2.0)	7.5(2.1)	5.9(3.3)	5.6(2.6)	8.3(1.2)	7.9(1.8)	0.027* ^{c,d,f,g,i,j,k,l}
Satisfaction	7.3(1.8)	6.4(2.0)	0.025*	7.5(1.9)	6.5(2.0)	6.9(1.4)	7.4(1.6)	6.0(2.3)	6.1(2.0)	0.140
Hopefulness	7.4(1.9)	6.1(2.4)	0.009**^{a}	7.7(1.6)	5.9(2.6)	7.2(1.5)	6.5(2.0)	5.9(2.7)	6.1(2.6)	0.063
Overall physical health	7.1(1.4)	6.0(1.6)	0.002**^{a}	7.5(1.3)	5.9(1.2)	6.6(1.2)	6.5(1.4)	6.1(1.7)	5.8(1.8)	0.004** ^{b,c,d,i,m,n}
Interference activities at home	5.8(2.8)	7.2(2.5)	0.022*^{a}	5.1(2.7)	8.2(1.7)	6.9(1.7)	6.3(3.1)	6.5(3.2)	7.4(2.4)	0.020* ^{b,c,d,e,k,l,m}

*$p<0.05$; **$p<0.01$
a = clinically relevant
Clinically relevant between cancer types:
b = testicular vs sarcoma
c = testicular vs gynaecologic
d = testicular vs other
e = gynaecologic vs sarcoma
f = gynaecologic vs breast
g = gynaecologic vs hematologic
h = sarcoma vs other
i = breast vs other
j = hematologic vs other
k = sarcoma vs breast
l = sarcoma vs hematologic
m = testicular vs breast
n = testicular vs hematologic

Table 4: (continued) Most important HRQoL items (mean (SD)) among AYA cancer patients (n=83) for treatment intention, partner and children

	Treatment intention			**Partner**			**Children**		
	Curative	**Palliative**	**P-value**	**Yes**	**No**	**P-value**	**Yes**	**No**	**P-value**
Support from others	8.1(1.8)	8.3(1.1)	0.745	8.4(1.5)	7.6(1.6)	0.038	7.8(1.8)	8.4(1.4)	0.102
Distress initial cancer diagnosis	7.4(2.6)	8.8(1.3)	0.071	7.9(2.3)	7.1(2.4)	0.166	8.2(2.1)	7.4(2.4)	0.122
Distress for family	7.5(2.1)	8.6(1.3)	0.076	7.7(2.0)	7.5(2.0)	0.764	7.7(1.7)	7.6(2.2)	0.858
Quality of life	7.4(1.5)	6.2(2.4)	0.006**[a]	7.4(1.6)	6.6(1.9)	0.073	7.3(1.7)	7.1(1.8)	0.715
Happiness	7.2(1.8)	6.2(2.4)	0.079	7.4(1.8)	6.2(2.0)	0.008**[a]	7.3(1.7)	7.0(2.0)	0.541
Cancer Treatment distress	6.8(2.4)	7.7(1.2)	0.224	7.1(2.3)	6.8(2.1)	0.610	7.0(2.4)	7.0(2.2)	0.972
Satisfaction	7.0(1.9)	6.2(2.4)	0.195	7.2(1.7)	6.0(2.2)	0.013*[a]	7.2(1.7)	6.6(2.0)	0.204
Hopefulness	7.1(1.9)	4.6(2.6)	0.000**[a]	7.0(2.1)	6.5(2.3)	0.320	6.7(2.3)	6.9(2.1)	0.715
Overall physical health	6.9(1.3)	4.8(1.9)	0.000**[a]	6.8(1.4)	6.0(2.0)	0.049*	6.7(1.5)	6.5(1.6)	0.603
Interference activities at home	6.4(2.8)	7.0(2.5)	0.448	6.4(2.8)	6.5(2.5)	0.856	6.3(2.6)	6.5(2.8)	0.784

positive feelings and thoughts, also called benefit finding, has been previously described and is associated with less HCP visits and lower levels of distress [20]. In our study, stratified analyses showed that male patients, patients being treated with curative intent and patients who have a partner valued mainly positive formulated HRQoL items higher.

Our results are in line with previous studies. Thompson *et al.* found that there is a significant gap between the identified health care preferences of AYA with cancer (15-25 years) and the understanding of the Australian oncology HCP who deliver their care. HCP significantly underestimated the breadth of AYA psychosocial concerns in AYA with cancer and had a strong focus on survival and physical wellbeing [16]. This is interesting because a study among older patients (mean age 55 years) found that there is considerable consistency between physicians' and patients' perceptions of the needs and support that the patients received. There was a discrepancy between the actual and the desired level of emotional and cognitive support [17]. In addition, Snyder *et al.* concluded that the issues cancer patients (mean age 61.5 years) prefer to be addressed, were the issues that HCP felt difficult to deal with [21].

A previous study among 294 long-term breast cancer survivors (almost 6 years after cancer diagnosis, mean age 50.9 years) using the QoL-CS questionnaire showed that survivors experienced, besides negative effects affecting overall quality of life, also benefits (hopefulness, having a life purpose, having a positive change after treatment) which helped to cope with worse outcomes [22]. In our study we also observed many of these positive effects, indicating that resilience and post-traumatic growth can be important consequences in the AYA population after cancer treatment [23,24].

Male AYA cancer patients scored clinically relevant higher on items concerning quality of life, happiness, hopefulness, overall physical health and experienced less interference with activities at home. This is line with a previous study where male gender showed a positive correlation with empowerment, which may be explained by the fact that men use more effective problem-focused coping strategies [25]. It could also be due to the fact that a substantial part of our study sample includes male patients with testicular cancer (34%) who, in general, have a good prognosis and a relatively short treatment duration. AYA patients with partner scored clinically relevant higher on happiness and satisfaction, which illustrates the buffering and stabilizing effect of the social support of a partner [26].

It is valuable to establish the HRQoL priorities of AYA cancer patients in order to prioritize the items where AYA needs specific attention for. The discrepancy between top ten HRQoL priorities between AYA and HCP illustrates that we also must invest in thorough listening to patients' needs and training and guidance of oncology HCP in delivering age adjusted psychosocial care. The results of this study will add in developing and spreading the knowledge about how AYA-specific care should be organized, mainly regarding topics about perceived support from others, distress about initial cancer diagnosis and distress for family. It also emphasizes the importance of patient experiences and needs in the development of age-specific health care [27]. Since 2013 the Dutch AYA 'Young and Cancer' Platform has been established, in co-participation with AYA cancer patients and HCP from university medical centres and large regional centres. The main goal of the Platform is to improve the care for and the quality of life of AYA cancer patients by developing structural, standardized, comprehensive and patient-centred guidelines for AYA cancer care, research and education. An e-module has been developed recently to educate students and health care professionals in the Netherlands on age specific topics relevant for AYA cancer patients. Better training of HCP can reduce discrepancies between patients and HCP supportive care needs.

We acknowledge several limitations of our study. First, AYA cancer patients evaluated their own situation and HCP evaluated the HRQoL of the AYA cancer patient population in general. Comparing patient-specific versus general data could have influenced the results. Data should therefore be interpreted with caution. Second, AYA cancer patients were treated in a single centre and received multidisciplinary care by a dedicated AYA team, while the HCP were from several centres. It could be that HRQoL item scores are better than those of AYA cancer patients treated in other centres in the Netherlands without age-specific care. The patients in the current study sample were diagnosed with a relatively advanced stage of disease and were treated intensively, mostly with more than one treatment modality. This is an overestimation in disease severity of the entire AYA cancer population [28]. Both factors limit the generalizability of the results of the current study. Third, the QoL-CS questionnaire is not an AYA-specific HRQoL questionnaire. It was validated in a sample of cancer survivors with a mean age of 49.6 years who were on average 6.7 years after cancer diagnosis [18]. Therefore, we assume that the QoL-CS questionnaire has less discriminative value in our AYA population as our sample was median 2.1 years after cancer diagnosis. Moreover, studies have shown that the meaning of patients' self-evaluations of their quality of life may not be the same across different points in time, a phenomenon known as response shift. It reflects change that occurs because of adaptation to cancer, not true change due to cancer progression [29]. This phenomenon could have influenced our results. A fourth limitation is the low response rate, which is not unusual in studies in young patients with cancer but was even lower than in previous questionnaire studies among AYA patients (29% response rate in the current study sample versus 43% and 52% in previous studies) [30,31]. Unfortunately, we do not have information regarding the reasons for not participating. Because demographic data were not collected from the non-responders, we could not rule out selection bias. A fifth limitation is that we have used the QoL-CS questionnaire in a group of oncology HCP. Since the QoL-CS questionnaire is validated in cancer survivors [18], one could question whether HCP interpret the questions in a similar way and whether HCP could estimate the effect on HRQoL items as they might treat only few patients with particular types of cancer instead of the broad variety in cancer types of the whole AYA population. Sixth, the HCP sample was relatively small and has only few physicians. Since data were gathered at an AYA seminar, one could assume that HCP in the sample are highly dedicated with care for AYA cancer patients, which could skew the data.

In conclusion, this study showed a incongruence between the views of AYA cancer patients and HCP regarding the most important HRQoL items. Overall, HCP in this study believed that the burden of cancer and its treatment is bigger than actually perceived by the patients themselves. Assessing HRQoL can therefore be of clinical importance in order to provide optimal age-specific care. The discrepancy between patients and HCP illustrates the importance of co-creation survivorship care together with patients in particular of this age group. Future research should aim at developing an age-specific questionnaire, which discriminates between positive and negative HRQoL items and its impact on overall HRQoL in AYA cancer patients.

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Chapter 3

Prevalence and correlates of high fear of cancer recurrence in late adolescents and young adults consulting a specialist Adolescent and Young Adult (AYA) cancer service

Belinda Thewes, Suzanne E.J. Kaal, Jose A.E. Custers, Eveliene Manten-Horst, Rosemarie Jansen, Petra Servaes, Winette T.A. van der Graaf, Judith B Prins, Olga Husson

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Abstract

Objective: High fear of cancer recurrence (FCR) is a frequently reported problem among cancer patients. Previous research has shown that younger age is associated with higher levels of FCR. However, little attention has been given to date about how FCR manifests itself among adolescent and young adult (AYA) cancer patients. This study explores the prevalence, correlates of high FCR and its association with HRQoL in cancer patients in their late adolescence or young adulthood.

Methods: Seventy-three AYA cancer patients, aged 18-35 years at diagnosis, consulting the AYA team of the Radboud University Medical Center completed questionnaires including the Cancer Worry Scale (CWS), Quality of Life-Cancer Survivors (QOL-CS) and Hospital Anxiety and Depression Scale (HADS). Socio-demographic and medical data was collected by self-reported questionnaire.

Results: Forty-five participants experienced high FCR (62%), which was higher than the 31-52% reported in previous studies among mixed adult cancer patient samples. Socio-demographic and medical variables were not associated with levels of FCR. High FCR was significantly associated with lower levels of social and psychological functioning and overall HRQoL and higher levels of anxiety and psychological distress.

Conclusion: Results illustrate that FCR is a significant problem amongst AYA cancer patients consulting an AYA team, with participants reporting higher levels of FCR than cancer patients of mixed ages. Health care providers should pay specific attention to this problem by screening and the provision of appropriate psychosocial care when needed.

Introduction

Recently national adolescent, and young adult (AYA) programs have been formed in an attempt to bridge the gap between the pediatric and adult oncology services and to address the unmet supportive care needs of the AYA cancer patient group. Definitions of the AYA have evolved over time and there are currently differing perspectives regarding the appropriate definition of the AYA age range between countries. In the United Kingdom AYAs are considered to be patients aged between 13-24 years. In the United States the spectrum of AYA includes patients aged 15-39 years of age, whilst in the Netherlands, where the present study was conducted, AYAs are typically defined as patients aged 18-35 years at cancer diagnosis [1,2]. Regardless of the specific definition of AYA, a cancer diagnosis may have profound effects on the lives of AYA cancer patients, interfering with the attainment of normal developmental milestones [3]. At a time when most AYAs are trying to make future plans for career, relationships and children, the future can seem uncertain. Furthermore, cancer-related issues such as premature confrontation with mortality, changes in physical appearance, increased dependence on parents, disruptions of social life and school/employment because of treatment, and potential loss of reproductive capacity may become particularly distressing and could negatively impact their health-related quality of life (HRQoL) [4,5,3,6]. Because the vast majority of AYA cancer patients will go on to be long-term survivors (relative 5-year survival of 82% [7]), it is important to optimize the quality of their survival.

Due to cancer occurring at a critical phase in life, AYA cancer patients (AYAs) have unique physical, psychological and social care needs [8,9]. Nevertheless, research involving AYAs aged 15-39 years at diagnosis reports a high number of unmet needs amongst AYAs, with psychosocial help for fear of cancer recurrence (FCR) as a key unmet need [10]. FCR has recently been defined as the 'fear, worry, or concern relating to the possibility that cancer will come back or progress' [11]. It has also been described as a 'sword of Damocles' that hangs over survivors for the rest of their lives [12]. While a normal level of FCR is adaptive because it can keep a person alert and aware of symptoms [13], high levels of FCR can adversely affect a person's HRQoL and social activities [14,15]. Cancer survivors with high levels FCR may engage in excessive monitoring for signs of potential recurrence and/or try to cognitively or behaviorally avoid reminders of their cancer [13]. High FCR is associated with both more unscheduled doctor appointments as well as unwillingness to be discharged from follow-up care [16-19], leading to increased health care costs [18]. Furthermore, patients with elevated FCR commonly report difficulties planning for the future [15], which may adversely impact on the developmental milestones of young adulthood although this has not been systematically investigated. Comparing of the prevalence of FCR across studies is difficult due to a lack of a consensus definition of high FCR [11]. However, a systematic review of FCR literature [14] suggests that moderate to high levels of FCR affect on average 49% of cancer patients and severe FCR affects on average 7% [14] and high levels of FCR persist over time when untreated [20]. Recent Dutch studies using the Cancer Worry Scale (CWS) report prevalence rates for high FCR of 31% in women breast cancer (n=194) [21], 36% amongst men with localized prostate cancer (n=283) [22], 38% in colorectal cancer patients (n=76) [23] and 52% in gastro-intestinal stromal tumor patients (GIST; n=54) [24]. Younger age is the most consistent predictor of increased FCR among cancer patients [20,14]. However, the majority of studies are conducted among breast cancer patients or mixed-aged adult samples. There is inconclusive evidence of the association between FCR and time since diagnosis or objective indices of risk of recurrence with some studies finding an association and others not [14]. To date, little data is available on the prevalence of FCR in the AYA population or the factors associated with increased levels of FCR in this age group. A recent study reported a FCR prevalence rate of 85.2% among AYA cancer patients aged 15-39 years. However, this study is limited by the fact that it used a single non-validated question to assess FCR and that it recruited a self-selected group who were users of a cancer survivorship website [25]. Studies involving cancer patients of mixed age show that FCR is associated with poorer HRQOL [14], and another recent study has shown that in AYA cancer patients this relationship is moderated by perceived growth [26].

This cross-sectional study explores the prevalence, correlates and association with HRQoL of FCR in a sample of consecutively-seen AYA cancer patients. A strength of the present study over existing research is that FCR is measured with a valid and reliable FCR-specific questionnaire with a cut-off for high FCR which has been validated in the Dutch adult cancer patient population [21,23,24]. A secondary aim was to compare the reported prevalence of FCR in the present sample to that of other studies of Dutch cancer survivors using the same outcome measure. Due to the fact that previous literature reports a consistent relationship between younger age and FCR, and AYAs experience cancer at a vulnerable phase of life where future goals are defined and coping skills need to be developed, it was hypothesized that AYAs would report a higher prevalence of FCR than has been reported in cancer patients of mixed ages (31-52%), participants with high FCR would have significantly lower HRQOL than with those with low FCR and that clinical characteristics would not be significantly associated with having high FCR.

Methods

Participants

Using the Dutch definition of AYA, patients aged 18-35 years at cancer diagnosis, who had been seen by at least one of the members of the AYA team of the Radboud University Medical Center (Raboudumc) in The Netherlands, were invited to participate in this study. The AYA team is a dedicated multidisciplinary team for patients aged 18 to 35 years at diagnosis including a medical oncologist, clinical nurse specialist, medical psychologist and a social worker. Patients consulting the AYA team receive regular medical care from their own treating specialist at Raboudumc (oncologist, surgeon, hematologist, dermatologist, urologist, gynecologist etc.) and visit the AYA team for age-specific questions and care needs. In general, patients visiting the AYA team represent a group of patients with high disease severity, diagnosed with relatively advanced stage of disease and undergoing intensive treatments, and reporting more problems with coping. Patients with lower stage disease (e.g. cervical cancer, melanoma) treated solely by surgery, are not often seen by the AYA team.

In order to depict the real-life heterogeneous sample of AYA cancer patients visiting the AYA team this study included, AYA patients independent of their treatment status (during or after treatment), type of treatment (surgery, chemotherapy, radiotherapy, immunotherapy and hormonal therapy or combination), or the number of visits to the AYA team. Inclusion commenced January 2012 and ended March 2016.

Procedure

Potential study participants were recruited via letters describing the study and inviting patients to participate in the study. Patients willing to participate had to actively opt-in to the study by providing written informed consent by email to a member of the AYA team. Participants were then sent a single set of questionnaires by email that could be completed online. The study was deemed exempt from full review and approval by a research ethics committee (CMO Regio Arnhem-Nijmegen).

Instruments

Sociodemographic and clinical characteristics

Demographic data, including age, gender, partnership, having children, living situation, educational level, and employment status were gathered by self-report. Medical data, including tumour type, disease stage, treatment type, treatment status (on/off treatment) and time since initial diagnosis were extracted from the patients' medical records by one of the researchers (SK).

Fear of cancer recurrence/progression

The Cancer Worry Scale (CWS) is used in research to assess concerns about developing cancer again (e.g. *how often do you worry about developing cancer (again)?*) and the impact of these concerns on daily functioning (e.g. *have these thoughts interfered with your ability to do daily activities?*) [21]. The CWS is a reliable (Cronbach's alpha in this study = .89) and valid measure of FCR which has been validated in several studies involving Dutch cancer patients [23,24,21,27]. The eight items of the CWS are rated on a four-point Likert scale ranging from *never* (1) to *almost always* (4). Scores range from 8 to 32 [28]. A cut-off scores of 13 or more is validated for prostate cancer survivors (sensitivity 86%; specificity 84%) [22], and 14 or more for breast (sensitivity 77%; specificity 81%)[21] and colorectal cancer survivors (sensitivity 86%; specificity 87%) [29] indicating high levels of FCR. The present study used a cut-off score of 14 or more to indicate high FCR.

Health-related quality of life

The Quality of Life for Cancer Survivors (QoL-CS) questionnaire was used to measure HRQoL. It consists of 41 items on the physical, psychological, social functioning and religious impact of cancer on the life of the patient. Respondents rate themselves along an interval rating scale ranging from 0 to 10 for each item. For subscale scoring purposes, all items were ordered, so that 0 indicated the lowest or worst possible HRQoL, and 10 indicated the highest or best possible HRQoL outcome. An overall QoL score was computed by averaging all 41 items [30]. Strong evidence for the validity and reliability of the instrument has been reported [31,32]. Cronbach's alphas ranged from 0.35 for religious functioning to 0.91 for the total QoL scale score in this sample.

Psychological distress

Psychological distress was measured with the Hospital Anxiety and Depression Scale (HADS). The HADS is a self-report questionnaire comprising 14 items on a four-point Likert-scale. Total score and subscales scores can be calculated for depression and anxiety (7 items each). Higher scores indicate more anxiety, depression, and psychological distress. Due to a lack of somatic items, the HADS is not confounded by the presence of physical symptoms and therefore suited for people with cancer [33]. The HADS is reliable [34] (Cronbach's alpha > 0.77 in this sample) and validated for use in different groups of Dutch subjects and in cancer patients [35,36].

Statistical analyses

The present study is a secondary analysis of a data collected to assess HRQOL amongst AYA cancer patients. Analyses were performed using Statistical Package for the Social Sciences version 22 (SPSS), and two-sided p values of <.05 were considered statistically significant. Differences in sociodemographic and clinical characteristics, HRQoL and psychological distress between patients with low and high levels of FCR were compared using chi-square and t-tests (or Mann Whitney U test), where appropriate. Given that a minimal clinically important difference for the primary outcome measure (CWS) has not been established, clinically meaningful differences were determined with Norman's 'rule of thumb', using ~0.5 SD difference to indicate a threshold discriminant difference in scores [37]. To contextualize the findings of the present study t-tests were used to compare mean levels of FCR reported in the present sample with the results of other Dutch cancer survivors studies using the CWS, and chi-square was used to compare the proportions reporting high FCR with other studies.

Results

Sample characteristics

In total, 309 letters requesting participation in the study were sent to AYA cancer patients visiting one of the members of the AYA team. Eighty-nine participants, comprising 57% of those who opted-in to the study (*n*=155) and 29% of those sent mailed invitations (n=309), completed the online questionnaire. Four participants were excluded since they were diagnosed with cancer under the age of 18 years. Twelve patients were excluded from analyses because they had a recent recurrence (n=5) or received palliative treatment (n=7), making the item wording of the CWS irrelevant to them, resulting in final sample of 73 participants. Table 1 displays socio-demographic and clinical and treatment-related characteristics of the sample. Mean age at cancer diagnosis was 27.4 years (SD=4.9) and average time since cancer diagnosis was 1.9 years (SD=2.6). The most common diagnosis was testicular cancer (34%), followed by breast cancer (15%) and sarcoma (12%). The majority of participants had undergone surgery (84%) and chemotherapy (86%), and had completed treatment at time of study (76%).

Table 1: Characteristics of the study sample stratified by level of FCR

	Total N= 73	Low FCR N= 28	High FCR N= 45	P-value
	n (%)[a]	n (%)[b]	n (%)[c]	
Gender				0.12
Male	36 (49%)	17 (61%)	19 (42%)	
Female	37 (51%)	11 (39%)	26 (58%)	
Age at diagnosis (yrs)	27.4 (4.6)	26.3 (4.9)	28.0 (4.4)	0.12
Time since cancer diagnosis (yrs)	1.9 (2.6)	1.9 (3.6)	1.9 (1.9)	0.94
Tumour type				0.53
Testicular cancer	25 (34%)	13 (46%)	12 (27%)	
Breast cancer	11 (15%)	2 (7%)	9 (20%)	
Sarcoma	9 (12%)	4 (14%)	5 (11%)	
Lymphoma	8 (11%)	2 (7%)	6 (13%)	
Gynecological	7 (10%)	3 (11%)	4 (9%)	
Melanoma	2 (3%)	0 (0%)	2 (4%)	
Leukemia	2 (3%)	1 (4%)	1 (2%)	
Other	9(12%)	3 (11%)	6 (13%)	
Stage				0.15
NA	8 (11%)	5 (18%)	3 (7%)	
Stage 1	12 (16%)	3 (11%)	9 (20%)	
Stage 2	23 (32%)	11 (39%)	12 (27%)	
Stage 3	11 (15%)	1 (4%)	10 (22%)	
Stage 4	13 (18%)	5 (18%)	8 (18%)	
Unknown	6 (8%)	3 (11%)	3 (7%)	
Treatment status				0.69
On	17 (24%)	6 (21%)	11 (26%)	
Off	54 (76%)	22 (79%)	32 (74%)	
Treatment type (yes)				
Surgery	61 (84%)	24 (86%)	37 (82%)	0.70
Chemotherapy	63 (86%)	25 (89%)	38 (84%)	0.56
Radiotherapy	20 (27%)	5 (18%)	15 (33%)	0.15
Immunotherapy	9 (12%)	0 (0%)	9 (20%)	0.01
Hormonal therapy	6 (8%)	1 (4%)	5 (11%)	0.25
Partner				0.51
Yes	52 (72%)	19 (68%)	33 (75%)	
No	20 (28%)	9 (32%)	11 (25%)	
Children				0.49
Yes	24 (33%)	8 (29%)	16 (36%)	
No	48 (67%)	20 (71%)	28 (64%)	
Living situation				0.13
With parents	12 (17%)	7 (25%)	5 (11%)	
On own	19 (26%)	9 (32%)	10 (23%)	
With partner	41 (57%)	12 (43%)	29 (66%)	
Highest completed education				0.58
Low	1 (1%)	0 (0%)	1 (2%)	
Intermediate	32 (44%)	14 (50%)	18 (41%)	
High	39 (54%)	14 (50%)	25 (57%)	
Employed or studying				0.91
Yes	63 (86%)	24 (86%)	39 (87%)	
No	10 (14%)	4 (14%)	6 (13%)	

NA= not applicable a= % of total participants; b=% of patients with low FCR; c=% of patients with high FCR

Table 2: Comparison of FCR levels as assessed with the CWS between AYA patients and mixed aged cancer patient samples

Author, Year	Sample characteristics n, cancer type, stages (localized, metastatic, mixed))	Age	Treatment status	Mean CWS (SD)	Results of tests comparing means with present sample	% scoring above diagnostic cut-off (≥14)	Results of tests comparing % above cut-off with present sample
Custers, 2014 [17]	N=194 patients with breast cancer treated with curative intents and disease-free at time study	Age at time of study: 57.0 (SD, 10.2) years (range, 30-88 years)	Completed hospital-based treatments Time since diagnosis (years): Mean 4.2, Range 1-11; SD2.3	13.4 (3.9)	t=2.78 mean difference=1.49 p=0.007 95%CI:0.42-2.56	31%	Difference=31% (95% CI = 19%-45%) X^2=22.81; p=<0.001
Custers 2016 [19]	N=76 patients with colorectal cancer treated with curative intents and disease-free at time study	Age at time of study: Median 67.3; range=41–88	Treatment status not reported Time since diagnosis: 1.3-9.2 years post surgery	12.5 (4.0)	t=4.46 mean difference=2.39 P=0.002 95%CI:1.32-3.46	38%	Difference=24% (95% CI = 9%-41%) X^2=9.20; p=0.002
Custers 2016 [20]	N=54 patients with localized or metastatic gastrointestinal stromal tumours	Age at time of study: Median 63.3; range 21 – 84	61% receiving active TKI treatment Time since diagnosis (years): Median 3.9; range 0.5–17	14.5 (5.2)	t=0.728 mean difference=0.39 p=0.47 95%CI:-0.68-1.46	52%	Difference=10% (95% CI = -6%-28%) X^2=1.59; p=0.21
Van de Wal, 2016 [18]	N=283 patients with localized prostate cancer treated with curative intent	Age at time of study: Median 70.0 (range 54–89)	Completed all hospital-based treatments Time since diagnosis(years): Median 7.9; range 0.9–20	12.0 (3.7)	t=5.39 mean difference=2.89 p=<0.001 95%CI:1.82-3.96	36%	Difference=27% (95% CI = 15%-39%) X^2=17.38; p=<0.001

CI= confidence interval; X^2=Chi-square

Prevalence FCR

Mean score on the CWS for the AYA cancer sample was 14.9 (SD=4.6). Forty-five AYA cancer patients (62%) scored 14 or higher on the CWS suggesting a high level of FCR. The percentage of AYA cancer patients scoring high on FCR was significantly higher than the 31% in breast cancer patients (t=2.8, p=0.007), 36% in prostate cancer patients (t=5.4, p=<0.001), 38% in colorectal cancer patients (t=4.5, p=0.002), but it did not differ significantly from 52% prevalence reported by GIST cancer patients (t=0.7, p=0.47) (Table 2).

Correlates of High FCR

There were no differences in sociodemographic (age, gender, partner, education, living situation, and occupational status) and clinical variables (type of tumor, type and phase of treatment, disease stage) between AYA cancer patients with high or low levels of FCR (Table 1). However, immunotherapy was significantly associated with high FCR (Chi^2= 6.7, p=.01).

Association between High FCR, HRQoL and psychological distress

AYA cancer patients with high FCR (CWS ≥ 14) reported worse functioning in the psychological domain (t=5.1; p<0.01), and social functioning domain (t=3.6; p<0.01), and lower overall HRQoL (t=4.5; p<0.01), compared with those with low levels of FCR (Table 3). These differences were clinically relevant as well as statistically significant. No differences were found for physical and religious functioning. AYA patients with high levels of FCR reported significantly higher scores on anxiety (t=-3.5; p<0.01), and total distress (t=-3.0; p<0.01), compared with those with lower levels of FCR. These differences were of clinical relevance. No significant difference was found for depression.

Table 3: HRQoL and psychological distress scores according to level of FCR

	Total N=73	Low FCR N=28	High FCR N=45	T-value	P-value
Quality of Life for Cancer Survivors					
Physical functioning	7.5 (1.6)	7.8 (1.7)	7.4 (1.4)	1.1	0.28
Psychological functioning	5.8 (1.5)	6.8 (1.1)	5.1 (1.4)	5.1	<0.01[a]
Social functioning	5.2 (1.4)	5.9 (1.4)	4.8 (1.2)	3.6	<0.01[a]
Religious functioning	3.9 (1.2)	4.1 (1.3)	3.7 (1.3)	1.3	0.20
Total	5.7 (1.1)	6.3 (1.0)	5.3 (1.0)	4.5	<0.01[a]
HADS					
Anxiety	6.3 (3.9)	4.4 (3.0)	7.5 (3.9)	-3.5	<0.01[a]
Depression	4.1 (3.5)	3.2 (3.3)	4.7 (3.5)	-1.8	0.08
Total psychological distress	10.4 (6.6)	7.6 (5.7)	12.2 (6.6)	-3.0	<0.01[a]

[a] Clinically relevant difference

Discussion

The present study is among the first to quantify the prevalence of high FCR in a sample of AYA cancer patients, aged 18-35 years at diagnosis who consulted at least one of the members of the multidisciplinary AYA team. High levels of FCR, were reported amongst 62% of participants in the present sample. Whilst there remains debate around definition of high FCR and a consensus definition of clinical FCR is currently under development [11], the results of the present study confirm our hypotheses that FCR, assessed with the CWS, is a common concern among AYA cancer patients and high FCR is more prevalent amongst AYAs than cancer patients of mixed ages and stages [24,21,23,22]. Consistent with past literature [20,14] and as hypothesised, objective determinants of poor prognosis were not significantly associated with FCR in the present sample.

High prevalence rates of clinical FCR have been reported in other studies involving younger patients with a good prognosis. For example, Thewes et al. [38] found that 70% of survivors aged 18-45 years at diagnosis with early-stage breast cancer reported clinical levels of FCR. Reasons for the higher prevalence in younger people with cancer are not well studied but in breast cancer survivors motherhood of young children, and the unexpected nature of life-threatening illness at an early age have been postulated [39,17]. There is some evidence that the relationship between age and FCR may also be, in part, mediated by the perceived physical, social or economic consequences of having a recurrence [39], anxiety [40,39], coping style [41] and self-efficacy [42]. Due to small sample size it was not possible to test mediators of FCR in the present sample, but future studies should explore this issue.

The prevalence of high FCR in the present AYA sample was significantly higher than has been previously reported amongst breast, prostate and colorectal cancer patients however it did not significantly differ from that reported amongst GIST patients [24]. Potential similarities between the GIST and AYA samples are that both groups included patients with poor prognosis, whereas the other samples included only patients treated with curative intent. Another potential explanation is that both AYA cancer and GIST are rare diseases, meaning that patients may have fewer social comparators and less information available to them, these factors might also contribute to increased uncertainty in GIST and AYA. Another possible explanation is that both groups included patients receiving novel targeted therapies. Targeted therapies are often associated with extended treatment duration and intensive monitoring for signs of treatment response or recurrence over longer periods of time than standard cancer treatments, due to the frequent checking for treatment response and/or recurrence over extended periods these treatments might contribute to higher levels of FCR [43]. Further research is required to better understand the relationship between novel cancer treatments and FCR.

Consistent with the results of several literature reviews exploring the factors associated with FCR, the present study found that higher FCR was associated with poorer psychological and social functioning and lower overall HRQoL [14,20]. Physical symptoms can serve as triggers for FCR [24] and previous research has shown an association between FCR and the presence of physical symptoms among people with mixed cancer types [44,14,20]. However, it is noteworthy that in the present study no association was found between FCR and physical HRQoL. This is in contrast to previous literature [14]. Interestingly, no difference was found between the proportions of patients reporting low versus high FCR for most conventional treatment modalities, with the exception of immunotherapy which was associated with higher FCR in the present sample.

In considering the results of the present study several potential limitations should be acknowledged. To determine the prevalence of FCR in the present study the higher (and more conservative) cut-off score for high FCR (13 vs. 14) was selected. A lower CWS cut-off score of 11 vs. 12 has been suggested for screening purposes [21], and a cut-off score of 12 vs 13 has been used to detect high FCR in male prostate cancer patients [22]. Further research is needed to validate both the CWS and other common measures of FCR in AYA cancer patients. Given the high prevalence of FCR in AYAs, the results of this study underline the importance of establishing a psychometrically sound FCR screening questionnaire with a cut-off score specifically validated for the AYA population.

The cross-sectional design limits the determination of causal associations between the study variables. Furthermore, due to the small sample size it was not possible to conduct multivariate analyses adjusting for confounding effects or to examine moderating or mediating factors. Although the role of clinical characteristics in FCR is inconsistent across studies, future studies involving larger samples are needed to determine whether the predictors identified in the present study are replicated when their effects are adjusted for the influence of age and clinical characteristics such as time since diagnosis, type of treatment, treatment status and comorbidities. As this was a secondary analysis data on psychiatric morbidity and trait anxiety were not available but future studies might consider including these as covariates to determine to what extent high comorbid with or influenced by psychiatric disorder or trait anxiety.

All participants received multidisciplinary care by a dedicated AYA team within an academic hospital setting. AYAs referred to this specialized team often present with more complex care needs and therefore it is unclear to what extent FCR levels reported in the present sample are representative of the level of FCR in the broader population. Patients in this sample were also diagnosed with relatively advanced stage of disease (18% in our sample compared to 4% stage 4 disease in total Dutch AYA population) and were treated with multiple treatment modalities. Lower stage cervical cancer, melanoma, and early-stage testicular cancer are usually treated only with surgery. Therefore, the present sample might overestimate the disease severity of the entire AYA cancer population and may have contributed to the high observed level of FCR in the present sample. Both factors may limit the generalizability of our results. Another limitation of our study is the low response rate, which is unfortunately not unusual in studies of young cancer patients [45], limiting the generalizability of our results. Longitudinal, population-based studies are needed to understand changes in FCR over the course of the cancer trajectory and to provide insights into the predictors of these changes. More research is also needed to identify the prevalence and predictors of higher FCR in a large representative sample of AYA cancer patients, including those in 15-18 year old age range.

With regard to instrumentation of HRQoL, the current study relied upon a generic instrument with limited use in study samples consisting of young patients. There are currently no valid or reliable HRQoL instruments available for the entire AYA age range. The QoL-CS was selected because qualitative research highlights the need for tools measuring age-specific impact of cancer, such as employment challenges, social isolation, sexual and relationship problems [46]. Internal consistency of the QoL-CS in the present sample was high for the total score (0.91) and good to acceptable for most subscales with the exception of religious functioning (0.35). Cultural differences in religiosity between the Netherlands and the United States (where the QoL-CS was originally developed) might account for this difference. More research is needed to validate existing HRQOL instruments specifically for the AYA population.

Although FCR is a growing area in the psycho-oncology literature relatively few studies to date have focused specifically on AYA cancer patients. This study is one of the first to explore the issue of FCR in an AYA cancer population using an FCR-specific questionnaire with a validated cut-off. The present study found a significantly higher prevalence of FCR in this specific group of AYA cancer patients and a higher prevalence than has been reported in previous studies involving cancer patients of mixed ages. Based on the results of the present study, it is recommended that clinicians give greater attention to FCR in the clinical care of AYAs. Where feasible validated screening measures can be routinely used to identify problematic levels of FCR [47,21]. Where routine screening of FCR is not feasible clinicians should routinely ask about and normalize the presence of FCR and use questions to further explore whether FCR is chronic or bothersome and if there is a need for help to manage FCR. Patients with severe or problematic may benefit from a growing number of evidence-based interventions for reducing high FCR [48-50] [51,49,52]. A better understanding of FCR in AYA cancer patients will help clinicians identify patients who are in need of (psychosocial) intervention and when to most effectively intervene. Existing interventions are yet to be evaluated in an exclusively AYA population. However, as the theoretical foundations of existing interventions are relevant to all age groups, is it very likely that the therapeutic techniques they contain are equally relevant to AYA cancer survivors. However, some minor modification of patient resources (e.g. peer videos, patient examples in handouts) may make existing interventions more appealing and accessible to a younger audience. Given the potential impact of FCR on the developmental milestones of AYAs, further quantitative and qualitative research is needed to explore the functional impact of FCR on the lives of AYA cancer patients and to validate common measures of FCR in AYA populations. Future studies may therefore benefit from using multi-dimensional scales to assess FCR.

Conflict of Interest

The authors have no conflicts of interest to declare.

Originality and Author Contributions

This manuscript is original research and it has not been submitted or published elsewhere. Each author has participated in the design, preparation and critical review of the manuscript and takes public responsibility for the article.

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Chapter 4

Prevalence and impact of severe fatigue in adolescent and young adult cancer patients in comparison with population-based controls

Hanneke Poort, Suzanne E.J. Kaal, Hans Knoop, Rosemarie Jansen, Judith B Prins, Eveliene Manten-Horst, Petra Servaes, Olga Husson, Winette T.A. van der Graaf

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Abstract

Background: The current study determined the prevalence of severe fatigue in Adolescent and Young Adult (AYA) cancer patients (aged 18-35 years at diagnosis) consulting a multidisciplinary AYA team in comparison with gender- and age-matched population-based controls. In addition, impact of severe fatigue on quality of life and related factors of fatigue severity were examined.

Methods: AYAs with cancer (*n*=83) completed questionnaires including the Checklist Individual Strength (CIS-fatigue), Quality of Life (QoL)-Cancer Survivor, Hospital Anxiety and Depression Scale (reflecting psychological distress), and the Cancer Worry Scale (reflecting fear of cancer recurrence or progression).

Results: The vast majority of participants had been treated with chemotherapy (87%) and had no active treatment at the time of participation (73.5%). Prevalence of severe fatigue (CIS-fatigue score ≥ 35) in AYAs with cancer (48%, *n*=40/83) was significantly higher in comparison with matched population-based controls (20%, *n*=49/249; p < .001). Severely fatigued AYAs with cancer reported lower QoL compared to non-severely fatigued AYAs with cancer (*p*'s < .05). Female gender, being unemployed, higher disease stage (III-IV) at diagnosis, receiving active treatment at the time of participation, being treated with palliative intent, having had radiotherapy, higher fear of recurrence or progression, and higher psychological distress were significantly correlated with fatigue severity (*p* < .05).

Conclusion: Severe fatigue based on a validated cut-off score was highly prevalent in this group of AYAs with cancer. QoL is significantly affected by severe fatigue, stressing the importance of detection and management of this symptom in those patients affected by a life-changing diagnosis of cancer in late adolescence or young adulthood.

Introduction

Compared to adults, a diagnosis of cancer in adolescents and young adults (AYAs) between the ages of 18 and 35 years is rare. Advances in early detection and improvements in cancer treatments have resulted in an overall 5-year survival rate exceeding 80% in AYAs [1]. While AYAs with cancer face challenges similar to adult cancer patients, those in the heart of their youth experience unique cancer-related challenges in addition to usual age-related developmental tasks. The combination of achieving normal developmental milestones and simultaneously coping with a life-changing diagnosis of cancer frequently leads to psychosocial issues among AYAs with cancer [2]. Several studies have documented higher levels of distress and lower quality of life (QoL) in AYAs with cancer in comparison with healthy matched peers or adult cancer patients [3-5]. Moreover, treatment-related symptoms (e.g. pain and fatigue) and late effects (e.g. second cancers and cardiovascular disease) can interfere with a healthy body image, establishing social relationships, or attaining levels of autonomy and independence. With the expected further gains in overall survival of AYA cancer, it is important to address persistent disease- and treatment-related symptoms that compromise several domains of QoL.

Cancer-related fatigue (CRF) is one of the most common and distressing symptoms reported by adult and childhood cancer patients both during and after cancer treatment [6, 7]. The most commonly used definition for CRF is formulated by the National Comprehensive Cancer Network (NCCN) and defines CRF as *"a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity that interferes with usual functioning"* [8]. The vast majority of studies on the prevalence and severity of CRF have been conducted in adult or childhood cancer patients and only a few studies evaluated fatigue severity in AYAs with cancer. Moreover, the limited AYA-specific studies did not attempt to report on clinically relevant levels of fatigue by using a validated cut-off for severe fatigue [4, 9].

Knowledge on the prevalence of severe fatigue in AYAs with cancer is important, as we know from studies in adult cancer patients that severe fatigue is associated with more functional impairments, lower QoL, and more distress [6, 10]. For AYAs with cancer, the impact of severe fatigue might be even more pronounced because it can interrupt developmental milestones such as completing education, finding first or pursuing employment, beginning a romantic relationship, or starting a family. Understanding factors related to severe fatigue among AYAs with cancer will help health care providers identify who is more likely to experience this symptom. In addition, it will help researchers to determine potential factors that could be addressed in interventions targeting fatigue.

The present study determined the prevalence of clinically relevant levels of fatigue in AYAs with cancer using a validated cut-off for severe fatigue and compared the proportion of severely fatigued cases with the proportion of severely fatigued cases in a sample of gender- and age-matched population-based controls. In addition, the impact of severe fatigue on QoL and potential sociodemographic, treatment-related, and psychological correlates of fatigue severity was explored. A cross-sectional approach was used for this study to gather descriptive information about the presence of clinically relevant levels of fatigue among AYAs with cancer.

Materials and methods

Patients

Patients aged 18-35 years at cancer diagnosis and who had been seen by at least one of the members of the AYA team of the Radboud university medical center, Nijmegen, The Netherlands, were invited to participate in this study. The AYA team is a dedicated multidisciplinary team including a medical oncologist, clinical nurse specialist, medical psychologist, and social worker. Patients consulting the AYA team receive regular medical care from their own treating specialist (oncologist, surgeon, haematologist, dermatologist, urologist, gynaecologist, etc.) and visit the AYA team for age-specific questions and care needs. In general, patients visiting the AYA team represent a group of patients with higher disease severity, diagnosed with relatively advanced stage of disease and undergoing intensive treatments, and reporting more problems with coping. The AYA team does not often see patients with low stage disease treated solely by surgery, such as in the case of thin melanomas.

To depict the real-life heterogeneous sample of AYAs with cancer visiting the AYA team, AYAs with cancer were included in this first study on the prevalence of severe fatigue regardless of treatment status (during or after treatment), type of treatment (surgery, chemotherapy, radiotherapy, immunotherapy, targeted therapy, hormonal therapy or combination), or the number of AYA team visits (some patients only had one introduction talk with one of the members of the team and did not receive specific care thereafter). Inclusion commenced January 2012 and ended March 2016.

Population-based controls

Population-based controls were derived from a cohort of panel members surveyed by CentERdata, a research institute at Tilburg University collecting data from a sample of more than 2000 Dutch households (http://www.centerdata.nl/en/). This CentERpanel represents the adult Dutch-speaking population with respect to demographic characteristics. Population-based controls provided self-reported data on age and gender and completed a multi-dimensional fatigue questionnaire (Checklist Individual Strength, see measures). They had no sickness absence in the workplace (0 days) in the month prior to filling in the questionnaires. Further information on the presence of physical or mental health conditions in population-based controls was not available.

Procedure

Potential study participants were recruited via letters describing the study and inviting patients to participate in the study. Patients willing to participate had to actively opt-in to the study by providing written informed consent by email to a member of the AYA team. Participants were then sent a single set of questionnaires by email that could be completed online. The study was deemed exempt from full review and approval by a research ethics committee (CMO Regio Arnhem-Nijmegen, #2016-2872).

Measures

AYAs with cancer completed a self-report questionnaire on sociodemographic data (i.e., age, gender, partner status, having children, education level, and employment status). A member of the AYA team (SK) extracted clinical data (i.e., cancer diagnosis, disease stage at diagnosis, time since initial cancer diagnosis, type(s) of treatment(s) received, duration of cancer treatment, treatment status at participation, and time since completion of cancer treatment) from patients' medical records. AYAs with cancer completed the following questionnaires, including a multi-dimensional fatigue questionnaire:

Checklist Individual Strength, subscale fatigue severity (CIS-fatigue). The subscale fatigue severity of the CIS consists of eight items scored on a 7-point Likert scale. Total CIS-fatigue scores can range from 8 to 56, with scores greater than 34 indicating clinically relevant levels of fatigue [11]. The CIS-fatigue has been used in previous studies examining severe fatigue in cancer patients during and after cancer treatment [12-14]. A cut-off was used to group AYAs with cancer into two groups to indicate severely fatigued (≥ 35) and non-severely fatigued patients (< 35).

Quality of Life-Cancer Survivor (QoL-CS). The QoL-CS consists of 41 items scored on a 10-point Likert scale and was used as a cancer-specific measure of QoL [15]. The impact of cancer diagnosis and treatment is assessed with four subscales, i.e., physical, social, psychological, and spiritual wellbeing. In addition to the four subscale scores, the total QoL score reflecting the average across all items was used in this study. Higher scores indicated better QoL for all subscales.

Hospital Anxiety and Depression Scale (HADS). The HADS consists of 14 items scored on a 4-point Likert scale [16]. The summed total HADS scores range from 0 to 42, and were used to reflect psychological distress in our sample of AYAs with cancer [17]. Higher total scores indicate more psychological distress.

Cancer Worry Scale (CWS). The CWS consists of eight items regarding concerns about cancer recurrence or progression of cancer. Items are scored on a 4-point Likert scale ranging from ‘never’ to ‘almost always’ [18]. Total CWS scores range from 8 to 32, and can be used to assess cancer worrying. Higher total scores indicate more fear of cancer recurrence or progression. Patients with a recent recurrence (*n*=5) or receiving treatment with palliative intent (*n*=7) did not complete the CWS because the item wording of this measure was irrelevant to them.

Statistical Analyses

To compare mean fatigue severity and the prevalence of severe fatigue in AYAs with cancer with population-based controls derived form the sample of CentERdata (*n*=1923), AYAs with cancer were matched on gender and age (within a range of 0 to 5 years) with 249 population-based controls. Given the relatively low proportion of CentERpanel members within the age range of our study sample, the highest possible ratio for matching AYAs with cancer to controls was 1:3. Precision matching was performed with STATA/SE. All other analyses were performed using SPSS Statistics (version 22.0). Descriptive statistics and frequencies concerning socio-demographic and clinical data were calculated. An independent samples *t*-test was used to compare fatigue severity scores between AYAs with cancer and matched population-based controls. We used a Chi-square test to compare the proportion of severely fatigued cases in AYAs with cancer and matched population-based controls. Pearson and

Point-Biserial correlations were calculated to examine associations between continuous variables or continuous and dichotomous variables, respectively. The significance level was set at .05. We did not adjust for multiple testing.

Results

In total, 309 letters requesting participation in the study were sent to AYAs with cancer visiting one of the members of the AYA team. The total sample of 89 participants comprised 57% of those who opted-in to the study (*n*=55) and 29% of all those solicited by mail (*n*=309). Six participants were excluded, four since they were diagnosed with cancer under the age of 18 years and two because they were aged above 35 years at diagnosis. Table 1 displays sociodemographic, disease and treatment-related characteristics of the final sample of 83 AYAs with cancer stratified by the presence of severe fatigue. Mean age at cancer diagnosis for the total sample was 27.3 years (SD 4.4) and mean time since cancer diagnosis was 2.1 years (SD 2.6). The most common diagnosis was testicular cancer (34%) followed by sarcoma (19%). Disease stage at diagnosis was known and applicable in 67 participants. Of those, 36 (54%) were diagnosed with early-stage disease (stages I-II) and 31 (46%) with late-stage disease (stages III-IV). The majority of participants had undergone surgery (*n*=70, 84%) and chemotherapy (*n*=72, 87%), but were not on active cancer treatment at the time of study participation (*n*=61, 73.5%). Mean duration of cancer treatment was 15.8 months (SD 20.6). For the subset of 61 patients not on active cancer treatment at the time of study participation, mean duration since completion of treatment was 17.5 months (SD 30.6)

Table 1. Characteristics of the study sample stratified by fatigue severity

Characteristics	**Total sample (*n*=83)**	**Non-severely fatigued patients (*n*=43)**	**Severely fatigued patients (*n*=40)**
Age at cancer diagnosis,			
mean (SD)	27.3 (4.4)	26.5 (4.6)	28.0 (4.1)
18-25 years	30 (36%)	18 (42%)	12 (30%)
26-35 years	53 (64%)	25 (58%)	28 (70%)
Age at participation,			
mean (SD)	29.4 (4.7)	28.7 (5.0)	30.2 (4.4)
18-25 years	19 (23%)	13 (30%)	6 (15%)
26-35 years	58 (70%)	27 (63%)	31 (77.5%)
> 35 years	6 (7%)	3 (7%)	3 (7.5%)
Gender			
Male	43 (52%)	30 (70%)	13 (32.5%)
Female	40 (48%)	13 (30%)	27 (67.5%)
Partner [a]			
Yes	58 (70%)	32 (74%)	26 (67%)
No	24 (29%)	11 (26%)	13 (33%)
Children [a]			
Yes	27 (33%)	30 (70%)	25 (64%)
No	55 (66%)	13 (30%)	14 (36%)
Highest completed education [a]			
Low	2 (2%)	0 (0%)	2 (5%)
Intermediate	36 (43%)	18 (42%)	18 (46%)
High	44 (53%)	25 (58%)	19 (49%)
Employed or studying [a]			
Yes	53 (64%)	37 (86%)	16 (40%)
No	26 (31%)	4 (9%)	22 (55%)
Other	3 (4%)	2 (5%)	1 (2.5%)
Cancer diagnosis			
Testicular cancer	28 (34%)	22 (51%)	6 (15%)
Sarcoma	16 (19%)	5 (12%)	11 (27.5%)
Breast cancer	10 (12%)	4 (9%)	6 (15%)
Haematological malignancy	10 (12%)	2 (5%)	8 (20%)
Gynaecological cancer	9 (11%)	5 (12%)	4 (10%)
Melanoma	3 (4%)	2 (5%)	1 (2.5%)
Other [b]	7 (8%)	3 (7%)	4 (10%)

Table 1. Continued

Characteristics	**Total sample (*n*=83)**	**Non-severely fatigued patients (*n*=43)**	**Severely fatigued patients (*n*=40)**
Cancer stage at diagnosis			
Not applicable	9 (11%)	3 (7%)	6 (15%)
Stage I	11 (13%)	6 (14%)	5 (12.5%)
Stage II	25 (30%)	18 (42%)	7 (17.5%)
Stage III	13 (16%)	3 (7%)	10 (25%)
Stage IV	18 (22%)	11 (26%)	7 (17.5%)
Unknown	7 (8%)	2 (5%)	5 (12.5%)
Time since cancer diagnosis, mean (SD) in years	2.1 (2.6)	2.0 (1.8)	2.2 (3.3)
Lifetime cancer treatment [c]			
Surgery	70 (84%)	38 (88%)	32 (80%)
Chemotherapy	72 (87%)	38 (88%)	34 (85%)
Radiotherapy	24 (29%)	10 (23%)	14 (35%)
Immuno- or targeted therapy	13 (16%)	5 (12%)	8 (20%)
Hormone therapy	7 (8%)	4 (9%)	3 (7.5%)
Duration of cancer treatment, mean (SD) in months	15.8 (20.6)	15.0 (22.1)	16.7 (19.2)
Intent of cancer treatment			
Curative	71 (85.5%)	40 (93%)	31 (77.5%)
Palliative	12 (14.5%)	3 (7%)	9 (22.5%)
Treatment status at participation			
No active treatment	61 (73.5%)	36 (83.7%)	25 (62.5%)
Active treatment	22 (26.5%)	7 (16.3%)	15 (37.5%)

[a] Information was not available for n = 1 AYA with cancer

[b] Including glioma (n=1), sigmoid carcinoma (n=1), oropharyngeal cancer (n=1), neuroendocrine tumor (n=1), lung cancer (n=1), salivary gland cancer (n=1), and adrenal gland cancer (n=1)

[c] Multiple answers possible.

Prevalence of severe fatigue and impact on quality of life

AYAs with cancer reported a significantly higher fatigue severity score than matched population-based controls (31.5, SD 11.8 versus 24.9, SD 10.5, respectively, $p < .001$). The prevalence of severe fatigue in AYAs with cancer was significantly higher in comparison with matched population-based controls (48%, n=40/83 versus 20%, n=49/249, respectively, $p < .001$). Severely fatigued AYAs with cancer reported significantly lower scores on all four QoL subscales (i.e., physical, social, psychological, and spiritual well-being) and on total QoL, compared to their non-severely fatigued counterparts ($p < .05$, see Table 2).

Table 2. Impact of severe fatigue on quality of life of AYAs with cancer

QoL-CS	Non-severely fatigued patients (*n* =43) mean (SD)	Severely fatigued patients (*n*=40) mean (SD)	Mean difference	Sig.
Physical well-being	8.28 (± 1.21)	6.57 (±1.49)	-1.71	.000**
Social well-being	5.41 (±1.33)	4.81 (±1.30)	-0.60	.042*
Psychological well-being	6.27 (±1.29)	4.90 (±1.59)	-1.37	.000**
Spiritual well-being	4.21 (±1.16)	3.29 (±1.36)	-0.92	.001**
Total QoL	6.12 (±0.82)	4.95 (±1.13)	-1.17	.000**

*Mean difference is significant at the 0.05 level. **Mean difference is significant at the 0.01 level.

Table 3. Correlates of fatigue severity in AYAs with cancer

Correlates	Correlation coefficients	N	Sig.
Sociodemographic variables			
Age at cancer diagnosis	.194	83	.079
Age at participation	.185	83	.093
Gender (male/female)	.336	83	.002**
Partner status (yes/no)	.118	82	.291
Children (yes/no)	-.122	82	.273
Employed or studying (yes/no)	.394	79	.000**
Disease and treatment-related variables			
Time since cancer diagnosis	.073	83	.513
Cancer stage at diagnosis (early/late)[a]	.322	67	.008*
Duration of cancer treatment	.087	81	.439
Cancer treatment at participation (yes/no)	-.227	83	.039*
Time since completion of cancer treatment	.060	61	.646
Intent of cancer treatment (curative/palliative)	.270	83	.013*
Surgery (yes/no)	.178	83	.108
Chemotherapy (yes/no)	.115	83	.302
Radiotherapy (yes/no)	-.242	83	.028*
Immuno- or targeted therapy (yes/no)	-.107	83	.336
Hormone therapy (yes/no)	.064	83	.563
Psychological variables			
Psychological distress (HADS total)	.553	83	.000**
Fear of recurrence or progression (CWS total)[b]	.340	71	.004**

*Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level.

[a] Cancer stage was unknown for n=7 AYAs with cancer and not applicable for n=9 AYAs with cancer.

[b] CWS was not administered to n=12 AYAs with cancer, because they either had a recurrence (n=5) or received treatment with palliative intent (n=7).

Sociodemographic, treatment-related, and psychosocial correlates of fatigue severity

Correlations are listed in Table 3. Higher psychological distress was strongly correlated to fatigue severity (*R* = .55; *p* < .001). Female gender, being unemployed (not having a job, sick leave or disablement insurance act), higher disease stage (III-IV) at diagnosis, and higher fear of recurrence or progression were moderate correlates (*R*'s 0.30 to 0.50; *p*'s < .01). In addition, receiving active treatment at the time of study participation, palliative intent of treatment and having had radiotherapy were weakly associated with fatigue severity (*R*'s 0.10 to 0.30; *p*'s < .05). No significant associations were observed between fatigue severity and the other sociodemographic, disease- and treatment related variables (see Table 3; *p*'s > .05).

Discussion

In this study, severe fatigue affected almost half of the AYAs with cancer. The prevalence of severe fatigue in AYAs with cancer was more than twice as high in AYAs with cancer than in gender- and age-matched population-based controls (48% versus 20%). Severe fatigue as assessed with the CIS-fatigue is more prevalent amongst AYAs with cancer than adult disease-free breast cancer patients 3 years after diagnosis (38%) [19]. The prevalence amongst AYAs with cancer corresponds more closely with findings from a study performed in adult cancer patients during cancer treatment with palliative intent (47%) [13], which is remarkable given the major difference in prognosis between these two patient groups. In our sample, only a minority of the participants (*n*=12, 14.5%) were classified as being treated with palliative intent at the time of participation. Reasons for the high prevalence of severe fatigue in AYAs with cancer have not been studied. One might postulate that, in contrast to adult cancer patients, the higher prevalence of severe fatigue originates from the unique combination of being diagnosed and treated for cancer and the developmental milestones AYAs are confronted with during adolescence and young adulthood.

Alternatively, the higher prevalence of severe fatigue reported by participants in our study could be the result of selection bias. We recruited AYAs with cancer that consulted a multidisciplinary AYA team. The fact that patients consulted a specialized AYA team most likely indicates that these patients had additional disease and/or treatment-related questions or problems, although not all patients had a need for continued and specific care by the AYA team after the first consultation. The percentage of patients having had chemotherapy as part of AYA cancer treatment was high (87%). This further supports the likelihood of selection bias in our sample and might overestimate disease severity of the entire AYA cancer patient population. Nonetheless, we can conclude that within the subset of AYAs with cancer consulting a multidisciplinary AYA team, the prevalence of severe fatigue is substantial.

Significant differences were found in physical, social, psychological, spiritual, and total QoL for severely fatigued AYAs with cancer in comparison with non-severely fatigued patients, which echoes previous studies reporting on the detrimental effects of severe fatigue in adult cancer patients [6, 10]. More psychological distress was a strong correlate of fatigue severity in the present study. In addition, more cancer worrying, female gender, and being unemployed were moderately related to fatigue severity. Geue et al. (2014) studied gender-specific differences in quality of life after AYA cancer and found lower QoL for women than men, including higher levels of fatigue [20]. The finding that more psychological distress and cancer worrying were associated with fatigue severity is in agreement with the impact of fatigue severity on QoL of AYAs with cancer in this study. However, given the cross-sectional design of our study we cannot draw conclusions on causality. This also limits interpreting the finding that being unemployed was linked to higher fatigue severity, although it may suggest that severely fatigued AYAs with cancer might not be able to find appropriate work. This emphasises the relevance of further research into this topic.

We only found weak or non-significant links between treatment-related variables and fatigue severity; receiving active treatment at the time of study participation, receiving treatment with palliative intent, and having had radiotherapy were significant but weakly related to fatigue severity. A moderate association was found between late-stage cancer at diagnosis and fatigue severity. In previous studies among adult cancer patients during and after treatment, fatigue appeared to be unrelated to disease-related variables, but the receipt of chemotherapy was associated with fatigue long after treatment [21]. A recently published review among breast cancer survivors after treatment also reported that survivors treated with chemotherapy were at higher risk for developing severe fatigue, as were those survivors with a higher disease stage at diagnosis [22]. As mentioned before, a noteworthy proportion of participants (87%) in our sample had been treated with chemotherapy.

The present study has several limitations. The sample size of our study was relatively small and the low participation rate increases the probability of bias by non-response. Unfortunately, small sample sizes are also seen in other studies in which patients of AYA age are asked to participate [23, 24]. Recruitment for our study took place over a period of 4 years. Additional efforts to increase data collection, such as multiple mailings of questionnaires or follow-up phone calls, were only made in the latter part of the study. Our response rate might have been higher when these efforts were made throughout the entire duration of the study. However, in the AYA HOPE study fewer than half of the eligible AYAs with cancer responded to questionnaires despite extensive efforts such as multiple mailings, phone calls, and financial incentives [25]. One way to overcome the low response rate in AYA cancer research might be the use of in-person contact and patient-preferred paper-pencil rather than online surveys as recently suggested by Rosenberg et al. [26]. Given the low incidence of cancer in AYAs between the ages of 18 to 35 years, recruitment from multiple institutions in an (inter)national AYA network could also aid the collection of larger samples. This would also increase the ability to generalize findings, which is limited in our study since we recruited patients at a single university medical center. While a broad range of potential correlates of fatigue severity was studied, we cannot rule out the involvement of other potentially relevant factors that have not been examined in this study. For example, sleep problems are strongly correlated with higher levels of fatigue in patients with cancer [27]. In addition, a low level of physical activity and pain are also correlated with cancer-related fatigue [28]. There is evidence that the effect of sleep problems on fatigue is mediated by pain [29]. Unfortunately, we did not include validated instruments to assess sleep problems, physical activity, and pain as potential correlates of fatigue severity in our sample, which is a significant limitation of the study. Notwithstanding these limitations, the present study is the first to apply a clinically relevant cut-off for severe fatigue in AYAs with cancer aged between 18 and 35 years at diagnosis.

In conclusion, given the high prevalence and significant impact of severe fatigue on quality of life of AYAs with cancer, health care providers should pay careful attention to this symptom. In particular, female AYAs with cancer, those with more advanced disease at diagnosis, higher levels of psychological distress, and more cancer worrying seem to experience higher levels of fatigue. The longer-term survivorship rates of AYA cancer illustrate the potential longevity of AYAs with cancer. It is therefore important to investigate the course and persistence of severe fatigue in AYAs with cancer in longitudinal, population-based studies. Such studies would also aid the development of age-specific interventions addressing persistent cancer-related fatigue in AYAs with cancer to enable full participation in society throughout survivorship. Although evidence-based interventions for the management of cancer-related fatigue in adult cancer survivors are available and recommended within guidelines issued by the American Society for Clinical Oncology [30], these interventions have not been tested extensively in AYAs with cancer. Researchers should investigate whether these interventions can also be successfully applied to alleviate persistent cancer-related fatigue, improve QoL, and facilitate participation in society for the understudied population of AYAs with cancer.

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Chapter 5

Post-traumatic growth and resilience in adolescent and young adult (AYA) cancer patients: an overview

Suzanne R. Greup, Suzanne E.J. Kaal, Rosemarie Jansen, Eveliene Manten-Horst, Melissa S.Y. Thong, Winette T.A. van der Graaf, Judith B. Prins, Olga Husson

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Abstract

Purpose: To provide an overview of the literature on post-traumatic growth (PTG) and resilience among adolescent and young adult (AYA) cancer patients.

Methods: A literature search in Embase, PsychInfo, Pubmed, Web of Science, Cochrane Library, and Cinahl was carried out. Thirteen articles met the predefined inclusion criteria.

Results: Qualitative interview studies showed that AYA cancer patients report PTG and resilience: PTG is described by AYA cancer patients in terms of benefit finding including changing view of life and feeling stronger and more confident, whereas resilience is described as a balance of several factors including stress and coping, goals, optimism, finding meaning, connection and belonging. Quantitative studies showed that sociodemographic and clinical characteristics were not associated with PTG. Enduring stress was negatively, and social support positively, associated with PTG. Symptom distress and defensive coping were negatively and adaptive cognitive coping was positively associated with resilience. Both PTG and resilience were positively associated with satisfaction with life and health-related quality of life (HRQoL). Resilience was found to be a mediator in the relationship between symptom distress and HRQoL.

Two interventions aiming to promote resilience, a stress management and a therapeutic music video-intervention, were not successful in significantly increasing overall resilience.

Conclusion: Most AYA cancer patients report at least some PTG or resilience. Correlates of PTG and resilience, including symptom distress, stress, coping, social support and physical activity, provide further insight to improve the effectiveness of interventions aimed at promoting these positive outcomes and potentially buffer negative outcomes.

Introduction

A common trend of incorporating data from adolescent and young adult (AYA) cancer patients into either childhood or older adult populations in research has created a gap in understanding the AYA cancer experience.[1] Adolescence and young adulthood is a complex developmental phase in life defined not only by significant physical changes, but also by critical psychosocial challenges, including transitioning to independence from parents, establishing autonomy and self-identity (personal set of goals and values), engaging in interpersonal relationships (e.g. intimacy, marriage, family forming), along with educational and employment decisions and attainments.[2] A cancer diagnosis during this unique phase of physical and psychosocial growth can disrupt the achievement of developmental milestones and have life-long repercussions. Research shows that AYA cancer patients demonstrate significantly worse health-related quality of life (HRQoL) and greater levels of psychological distress compared to healthy matched peers, due to these challenging circumstances.[3]

Over the past decade, psychosocial research has broadened its scope from the negative aftermath of traumatic events,[4, 5] such as a cancer diagnosis, to the identification of positive outcomes or positive ways in which people's lives have changed as a result of a struggle with adversity.[6, 7] Post-traumatic growth (PTG) is described as the positive psychological change that appears following significantly burdensome or traumatic life events. Specifically, people who have been exposed to trauma reported PTG in relationships, in their outlook on life, in their perception of themselves, in their spiritual beliefs and lastly in their appreciation of life.[8] A vast body of research shows that the majority of people who have been exposed to a potentially traumatic event are resilient.[9] Resilience is the ability to cope with negative emotions that arise from a stressful experience, by identifying and developing resources to function.[10] Many studies on PTG have explicitly or implicitly equated PTG with resilience or have even gone a step further and considered PTG superior to resilient outcomes.[11] For instance, Carver discriminated between PTG and resilience by defining resilience as a return to the prior level of functioning after difficulty and by relating PTG with not only returning to the prior level but exceeding it.[12] This definition assumes that for PTG to occur, a person has to demonstrate resilience and return to a healthy functioning level before higher, even more efficient functioning levels can be reached. Tedeschi and Calhoun (1995) supported this assumption.[13] They state that positive outcomes after traumatic life events depend on the coming together of several personal variables, resilience being one of them. Hence, for PTG to develop, a person needs to not only be for example optimistic, hardy, and face life crises that represent irreversible changes, but they also need to be resilient in order for a new level of adaptation to be achieved. Westphal and Bonanno (2007) objected to the notion that resilience is often equated with PTG and suggest that PTG and resilience should be viewed as two independent constructs.[14] They have even gone a step further and argued that it is very unlikely for resilient persons to perform the meaning making behaviours that are related to PTG since they do not struggle to the same extent as other, more traumatised persons would. Thus, survivors of trauma that are highly resilient will not engage in the cognitive processing that is essential for PTG to develop.[14] Up to now there is little understanding of the relation between PTG and resilience and no empirical research thus far has tried to shed more light onto this association. Although PTG and resilience can both be seen as outcome as well as a process, the terms cannot be used interchangeably: PTG does not develop as a direct consequence of the traumatic experience but in the aftermath of it and in the struggle to find a new normal,[15, 16] while resilience indicates the ability to cope with negative emotions that arise from a stressful experience and function at normal or close to normal capacity (maintain a stable equilibrium).[17] Nevertheless, there is some evidence that both, PTG and resilience, can function as protective factors counterbalancing the stress-related adverse effects of cancer and thereby improving HRQoL of patients.[18, 19] It may therefore be argued that interventions to improve psychological adaptation after cancer are not just about preventing, reducing, and/or treating psychological distress but also about increasing resilience and promoting PTG.[20] Until now, there has been little examination of PTG and resilience outcomes in AYA cancer patients. This review study aims to provide an overview of the literature on PTG and resilience experiences, correlates and interventions among AYA cancer patients to inform future research.

Methods

Search strategy

A computerized search of the literature through Embase (1974 - present), PsychInfo (1806 - present), Pubmed (1946 - present), Web of Science (1945 - present), Cochrane Library, including Cochrane Central Register of Controlled Trials (CENTRAL) and Cinahl (1981-present, EBSCOhost) was carried out by two researchers (SG and OH) on November 30th 2016. The search strategy combined the terms ('neoplasm' or 'cancer') and ('adolescent' or 'young adult') with other key terms related to positive psychosocial outcomes including ('posttraumatic growth' or 'relating to others' or 'new possibilities' or 'spiritual change' or 'life appreciation' or 'personal strength' or 'empowerment' or 'emotional growth' or 'resilience' or 'benefit finding' or 'positive health'). The reference lists of all identified publications were examined to find relevant publications not identified via the search strategy. There were no limits with regard to the year of publication. The search yielded 264 unique hits.

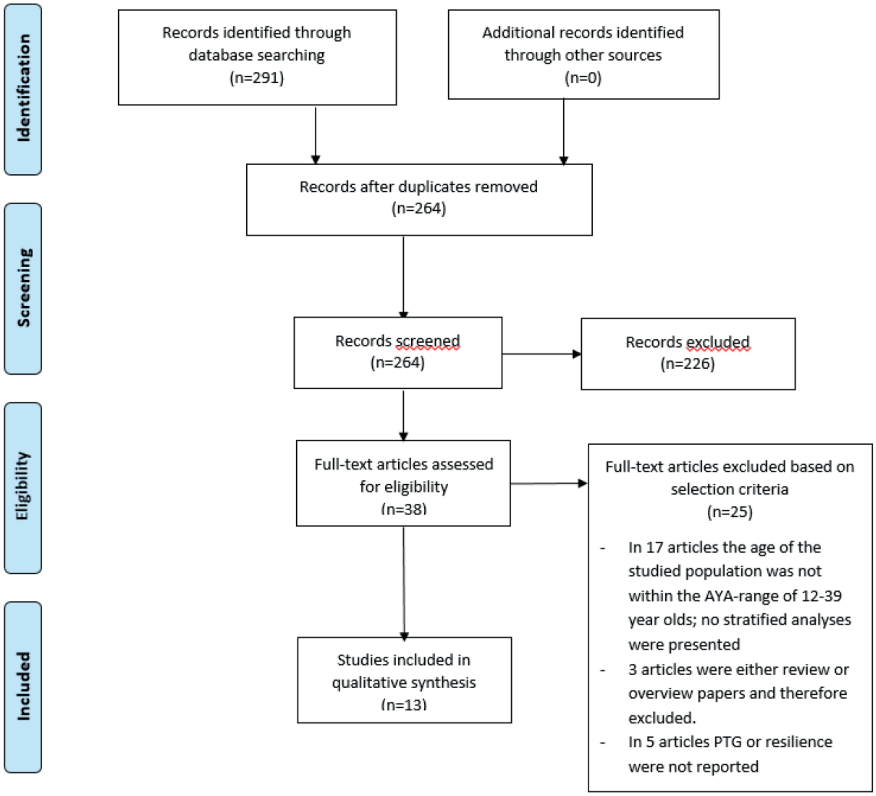
Selection criteria

We used an inclusive approach with regard to the AYA cancer patient age definition. Several AYA age definitions are used globally, ranging from 12 years[21] to 39 years,[22] based on physical and psychological developmental phase and accompanied care system (pediatric vs. adult oncology), aspects of tumor pathology or biology, or on health outcomes.[23] All studies that presented results of patients who were within the age range of 12 to 39 years at time of cancer diagnosis were included. Furthermore, studies were included: (i) if PTG or resilience (according to the definition of the researchers) was assessed; (ii) if the publication was an original article published in English (no poster abstract, letter to the editor or systematic review paper). Studies were excluded if: (i) they focused solely on pediatric and/or adult cancer patients; (ii) the study included patients of all ages but did not present the AYA patient data separately. The described inclusion and exclusion criteria were applied to the initial 264 hits. SG and OH screened all titles and abstracts, 38 articles met the criteria. After careful independent review by SG and OH, 13 articles meeting our selection criteria were included in our review. Figure 1 presents the flow-chart of the selection procedure.

Quality assessment

The methodological quality of the 13 included studies was independently assessed by two reviewers (SG and OH) based on established criteria for systematic reviews (Table 1).[24] The quality of a study can be described in terms of internal (methods) and external validity (representativeness and generalization). To cover both validity aspects the quality criteria were divided into 4 categories: assessment of outcomes, study population, study design and presentation of results. it was discussed in a meeting. For each quality criterion a study met, 1 point was assigned (highest possible score of 12 points). If a study did not meet our criteria or was described insufficiently or not at all, 0 points were assigned. Studies scoring 9 points or more were arbitrarily considered to be of 'high quality'. Studies scoring between 6-8 points were rated as 'adequate quality'. Studies scoring <6 points were rated as 'low quality'.

Figure 1: Prisma flow-chart of selection procedure



Results

Study characteristics

In total, 13 studies were included, all published between February 2007 and February 2015. Qualitative (n=3), quantitative (cross-sectional cohort, n=8) as well as intervention studies (n=2) were present. The main findings are summarized in Table 2.

Methodological quality and issues

The quality scores ranged from 3 to 10.5 points (Table 1), and the mean quality score of all studies was 7.8 points. The Kappa inter rater agreement was 0.66 (standard error of 0.16), indicating a good strength of agreement between the two independent reviewers.[25] Three studies were of low, four of high and six of adequate quality. General limitations of the included studies were patient response rates under 75% (n=10), small patient sample sizes (n=7) and lack of longitudinally gathered data (n=8) or group comparisons (n=6). A complicating factor for data extraction was that PTG and/or resilience were often secondary outcomes in most of the quantitative studies, resulting in a limited presentation of the results for these outcomes. We will discuss the main results of the included studies according to their study design.

Qualitative studies

Three qualitative semi-structured interview studies were included in this review.[26-28] These studies showed that AYAs with cancer have the capacity to be resilient[26] and almost all patients included in the studies reported some form of PTG.[27, 28]

AYAs with cancer described resilience as a balance of several factors including a) coping and stress; b) goals, purpose and planning; c) optimism; d) meaning and gratefulness; and e) connection and belonging.[26] The balance of these factors could promoted by increasing specific skills (including benefit-finding, goal-setting, stress management).[26] For example, AYA cancer patients who were able to find meaning, stay positive, set goals, control stress, seemed to consider themselves resilient, but in periods of extreme anxiety or transition (for example when they did not know what to expect), they felt their resilience diminished. Similarly, AYA cancer patients who persisted in negative emotions or who could not built purpose or meaning perceived themselves little resilient. AYA cancer patients stated that levels of resilience shifted with specific experiences, moods and skills.

Table 1: Quality scores of included studies (positive with respect to)

	Rosenberg, 2014	**Wicks, 2010**	**Wallace, 2007**	**Zebrack, 2015**	**Salsman, 2014**	**Monteiro, 2013**	**Seitz, 2011**	**Love, 2011**	**Wu, 2015**	**Wu, 2013**	**Smorti, 2012**	**Rosenberg, 2015**	**Robb, 2014**
Assessment of PTG / resilience													
1. A valid quality questionnaire is used for measuring PTG or resilience	0	0	0	1	1	1	1	1	1	1	1	1	0,5
Study population													
2. A description is included of at least two socio-demographic variables (e.g., age, employment status, educational status)	1	1	1	1	1	1	1	1	1	1	0	1	1
3. A description is included of at least two clinical variables of the described patient population (e.g., tumour, stage at diagnosis)	0	1	1	1	1	1	1	1	0	1	0	1	1
4. Inclusion and/or exclusion criteria are described	1	1	1	1	1	1	1	1	1	1	1	1	1
5. Participation and response rates for patient groups have to be described and have to be more than 75%	1	0	0	1	0	0	0	0	0	0	1	0	0
6. Information is given about the ratio of respondents versus non-respondents (0.5 point for reasons of non-response, 0.5 point for comparison of the responding vs. non-responding group)	0.5	0,5	0	0,5	0	0	0,5	0	0,5	0	1	0,5	0,5
Study design													
7. The study size is consisting of at least 50 patients (arbitrarily chosen)	0	0	0	1	1	0	1	1	0	1	0	0	1
8. The collection of data is longitudinally gathered	1	0	0	1	0	0	0	0	0	0	0	1	1
9. The process of data collection is described (e.g., interview or self- report etc.)	1	1	1	1	1	0,5	1	1	1	1	1	1	1

Table 1: Continued

Results													
10. The results are compared between two groups or more (e.g., healthy population, groups with different treatment or age) and/or results are compared with at least two time points (e.g., longitudinally versus post-treatment).	0	0	0	0	1	1	1	1	0	0	1	1	1
11. Mean, median, standard deviations or percentages are reported for the most important outcome measures	0	0	0	1	1	1	1	1	1	1	1	1	1
12. Statistical proof for the findings is reported	0	0	0	1	1	1	1	1	1	1	1	1	1
Total	5,5	4,5	4	10,5	9	7,5	9,5	9	6,5	8	8	9,5	10

PTG: post-traumatic growth

Table 2: Overview of all included studies

Author, year, country	Design	Sample	Age at time cancer diagnosis (years)	Age at time study (years)	PTG/resilience measure	Scores of positive outcome measures in studied population	Main results/conclusion	Quality
Qualitative studies								
Rosenberg, 2014, USA	Qualitative	17 AYAs requiring chemotherapy and diagnosed 14-60 days before study enrollment	14-22	15-23 (M=17)	Semi-structured interview at baseline and 3-6 months later to inform development of resilience promoting intervention	n.a.	AYAs perceived resilience as a balance that may be promoted by learned skills in stress- management, goal-setting and benefit-finding.	Low
Wicks, 2010, New Zealand	Qualitative	10 AYAs	12-19	16-22	In-depth semi- structured interviews into the 'adolescent cancer experience'	n.a.	Nine out of ten patients experienced a benefit finding after cancer.	Low
Wallace, 2007, UK	Qualitative	6 female AYAs	12-16	14-19	Semi-structured interviews focused on altered appearance	n.a.	All patients experienced benefit finding after cancer.	Low
Quantitative studies – PTG								
Zebrack, 2014, USA	Cross-sectional	165 AYAs in-treatment	14-39 (M=22.8)	15-40	PTGI: 21-item questionnaire with five subscales with total score range of 0- 105 points. Cronbachs α=0.95	Mean PTG score was 67.3 (SD=24.3)	PTGI total score did not vary by gender, race, relationship status, age, and severity of disease. No significant relationship between PTG and PTS was noticed at the 12-month follow-up. A curvilinear relationship between re-experiencing and two of the five PTG-subscales was observed.	High
Salsman, 2014, USA	Cross-sectional	335 AYAs within 0-60 months post treatment	18-39 (M=31.8)	18-44	PTGI-SF: 10-item version of the PTGI with range of 0-50 points α=0.92	Mean PTG score was 27.75 in patient group versus 27.22 for healthy controls (p=0.74)	Amount of PTG did not differ significantly between AYA cancer patients and the healthy controls.	High
Monteiro, 2013, Portugal	Cross-sectional	36 AYAs: 11 were in- treatment, 25 off-treatment	15-39	20-38 (M=28.5)	Personal Growth subscale of the PWBS: 14-item scale with range of 14-84. Cronbachs α=0.83	Mean personal growth score of the in-treatment	Cancer patients on-treatment scored significantly lower on personal growth than the off-treatment and healthy control groups.	Adequate

Table 2: Continued

						AYAs was 65.81(SD=6.35), of the off- treatment AYAs was 72.77(SD=7.89) and in healthy controls 71.27(SD=8.90)		
Seitz, 2010, Germany	Cross-sectional	820 long-term AYA cancer survivors	15-18	18-42 (M=30.4, SD=6)	PTGI Cronbachs α=0.89	Scores of PTG were not reported	PTG is positively associated both general and health-related life satisfaction.	High
Love, 2010, Canada	Cross-sectional	64 AYA cancer survivors	18-38	20-39 (M=28.8)	PTGI Scores range 1-6 Cronbachs α=0.90	Mean overall PTG score was 4.06(SD=1.08)	PTG scores did not vary by age, gender, and stage/severity of the disease. Stress (β=-0.04) and social support (β=0.46) were significantly associated with PTG (R^2=0.24).This association was stronger in physically inactive AYAs.	High
Quantitative studies – Resilience								
Wu, 2015, USA	Cross-sectional	40 AYAs in-treatment	13-20 (M=16-4)	13-20 (M=16-4)	RS: 25-item questionnaire with score range of 25-175. A score >147 indicates highly resilient, 121-146 medium resilient and <121 little resilient. Cronbach's α=0.93	Mean resilience score was 134.62 (SD=25.43)	Cancer symptom distress had a significant negative influence (β=-0.44) on resilience. Resilience mediates (buffer) the relationship between cancer distress symptoms and quality of life.	Adequate
Wu, 2013, Taiwan	Cross-sectional	131 AYAs receiving chemotherapy	11-19 (M=14.7)	11-19 (M=14.7)	HARS: 13-item version with range of 13-78. Cronbachs α=0.85	Mean resilience was 61.40(SD=10.28)	Age, time since diagnosis and school grade were not associated with resilience. Cognitive coping mechanisms are associated with higher levels of resilience, and defensive coping with more worries and less resilience.	Adequate

Table 2: Continued

Smorti, 2012, Italy	Cross-sectional	32 AYAs with bone cancer who were in complete remission after treatment	Not presented	11-20 (M=15.2)	Expectations for Future scale: 9-item scale with range of 9-45. Cronbach's α=0.78. Ego-Resiliency Scale: 10-item scale with range 10-40 points. Cronbachs α=0.79	Mean resilience score of AYAs was 26.94(SD=4.51) versus 31.13(SD=4.27) in healthy controls (p=<0.001)	AYA with cancer scored significantly lower on resilience than the healthy controls. Expectations of the future and resilience were significant and negatively correlated, openness to experience and resilience were significant and positively correlated.	Adequate
Intervention studies - Resilience								
Rosenberg, 2015, USA	Intervention (pre-post design)	15 AYAs diagnosed with cancer at least two weeks before study	12-25	14-25 (M=16.2)	CD-RISC: 10-item with range 0-40. Cronbachs α=0.85 Measured at baseline and follow-up	Mean resilience score at baseline was 26.2. Mean score at follow up after intervention was 28.4 (p=0.195)	The intervention was feasible and well-accepted by AYAs, however efficacy could not be determined	High
Robb, 2014, USA	Intervention (RCT)	113 AYAs undergoing hematopoietic stem cell transplantation	11-24 (M=17.3)	11-24 (M=17.3)	HARS: 15-item version with range 1-6 Cronbach's α=0.81. Measured at baseline (T1), post-intervention (T2) and 100 days post-transplant (T3)	Mean resilience score atbaseline was 5.1(SD=0.6)	Overall resilience did not differ significantly between the two groups at T2 (p=0.35), nor at T3 (p=0.29), although the intervention group reported better courageous coping (p=0.03) at T2 and better social integration p=0.028) and family-environment (p=0.008) at T3	High

CD-RISC: Connor-Davidson Resilience Scale; HARS: Haase's Adolescent Resilience Scale; M: mean; n.a.: not applicable; PTGI: Posttraumatic Growth Inventory; PTGI-SF: Posttraumatic Growth Inventory Short Form; PTS: post-traumatic stress; PWBS: Psychological Well Being Scale; RIM: Resilience in Illness Model; RS: Resilience Scale; YLOT: Youth Life Orientation Test; AYA, adolescent and young adult
SD, standard deviation

The other two interview studies focused on PTG which was described more in terms of benefit finding.[27, 28] Two recurrent themes emerged for the adolescent cancer experience: 1) loss of control, which resulted in anger or frustration and treatment non-adherence; and (2) benefit finding including improved bolstered relationships and improved personal attributes. All AYA cancer patients interviewed, except one, stated that they experienced at least one positive facet of being diagnosed with and treated for cancer.[27] This was supported by the results of another study, showing that AYAs with cancer perceived that their view of life had been changed in a positive way.[28] They felt stronger through having survived cancer. They felt this had weaponed them with the confidence and the faith that they could deal more effectively with other stressful situations.

Quantitative studies

Eight cohort studies, all with a cross-sectional design,[18, 29-35] and two intervention studies were included in this review.[36, 37]

Measures

Different questionnaires were used to assess PTG and resilience. Most of the questionnaires were not specifically developed for AYAs with cancer, however in most cases the reported psychometric properties were good.

Four of the five studies focusing on PTG used the Posttraumatic Growth Inventory (PTGI)[29-31] or its short form.[32] The PTGI is a well-validated 21-item questionnaire including factors of New Possibilities, Relating to Others, Personal Strength, Spiritual Change, and Appreciation of Life.[38] The questionnaire measures how successful individuals, coping with the aftermath of trauma, are in rebuilding or strengthening their perceptions of their self and others, and the meaning of events. A recent study showed that the PTGI was clear, appropriate, and relevant for AYAs with cancer.[39] One study used the personal growth scale of the Psychological Well Being Scale (PWBS). A theoretical model shows that psychological well-being consists of six specific dimensions of health: Autonomy, Environmental Mastery, Personal Growth, Positive Relations With Others, Purpose in Life, Self-Acceptance.[40] The personal growth scale is not validated among AYAs with cancer and it is limited by only measuring one aspect of PTG. Two of the five studies focusing on resilience used the Haase Adolescent Resilience in Illness Scale (HARS), [30,33] which measures how adolescents with an illness think or feel about managing their health after diagnosis of the disease.[10] The Ego-Resiliency Scale was used in one study[34] and is based on the concept of ego-resiliency or the ability to adapt one's level of emotional control up or down appropriate to the conditions.[41] Another study assessed resilience with the Resilience Scale (RS),[18] which had the best psychometric properties to measure resilience among adolescent populations.[42] The RS focuses on psychological qualities rather than deficits (e.g. personal competence and acceptance of self and life).[43] The last study used the Connor-Davidson Resilience Scale (CD-RISC),[29] measuring five dimensions of resilience: (1) personal competence; (2) trust in one's intuition, tolerance of negative emotions, and strengthening effects of stress; (3) secure relationships and positive acceptance of change; (4) control; (5) spiritual effects.[44]

PTG/resilience levels of AYAs with cancer compared to healthy controls

Mean PTG and resilience levels of AYAs with cancer are described per study in Table 2. Two studies compared the levels of PTG of AYAs with cancer with those of healthy controls.[32, 35] In the first study, the in-treatment group of AYA cancer patients scored significantly lower compared to age-matched healthy controls and off-treatment AYA cancer patients on PTG as measured by the personal growth subscale of the psychological well-being scale (PWBS).[35] In the other study, PTG levels as measured by the Posttraumatic Growth Inventory (PTGI) of AYA cancer patients did not differ from healthy controls matched on age, gender, educational level and partnership status.[32]

With respect to resilience, one study found that AYA cancer patients had a significantly lower resilience score compared to gender- and age-matched healthy controls on the Ego Resilience scale.[34]

Correlates of PTG/resilience

Six studies examined the correlates of PTG or resilience.[18,29,30,33-35] Socio-demographic and clinical characteristics were not associated with PTG. PTG scores did not vary by age, gender, stage/severity of the disease,[29, 30] race, relationship status, and treatment status, except for the PTGI subscale of 'New Possibilities', of which the score was slightly lower in Caucasian patients compared to non-white patients.[30] In another study, personal growth scores of the PWBS were compared between the in- and off-treatment AYA cancer patient age groups 15-20, 21-29 and 30-39 years, but no significant differences were found.[35]

Some evidence was found for an association between psychosocial factors and PTG. Stress (negative) and social support (positive) were significantly associated with PTG.[29] A significant interaction was found between physical activity and social support, indicating a strong positive association between social support and PTG in inactive persons and a weaker association for active persons. There is a lack of studies examining the clinical and sociodemographic correlates of resilience among AYAs with cancer. Only one study showed that age, time since diagnosis and school grade were not correlated with resilience.[33] This same study found that usage of a cognitive coping strategy to be associated with higher levels of resilience and usage of a defensive coping strategy to be associated with lower levels of resilience. However, no significant association between coping style and resilience was found in another study.[34] In this study a significant negative association between expectations of the future and resilience, and significant positive associations between resilience and openness to experience and impulse control was found. In addition, cancer symptom distress was negatively associated with resilience.[18]

Association PTG/resilience with other outcomes

Three studies examined the association between PTG or resilience and other outcome measures.[18, 30, 31] No significant relationship between PTG and overall post-traumatic stress (PTS) severity was observed.[30] However, curvilinear relationships between re-experiencing (a PTS symptom) and two of five PTG indicators (New Possibilities, Personal Strengths) were found, indicating some degree of distress related to the cancer experience was needed to develop PTG.[30] Another study found that PTG was positively associated with both general and health-related life satisfaction.[31]

Resilience was found to be a mediator in the relation between HRQoL and cancer symptom distress, indicating that resilience might play a role in limiting the adverse effects of cancer symptoms on HRQoL.[18]

Intervention studies

Two intervention studies were included.[36, 37] The Promoting Resilience in Stress Management (PRISM) intervention consisted of two long or four short skill-based modules focused on managing stress (stress management/coping and goal setting) and building resilience (cognitive restructuring and benefit-finding).[36] Although a small effect size was found, the scores before and after intervention did not differ significantly. The second intervention, a Therapeutic Music Video (TMV) aimed to (a) increase protective factors like hope-derived meaning, courageous coping, spiritual feelings, family environment and social integration; (b) diminish risk factors like defensive coping and illness-related distress; and (c) increase levels of resilience and self-transcendence.[37] AYAs with cancer were randomly allocated to either the TMV-intervention or a low dose audio book control group, both under supervision of a therapist, and completed six sessions over three weeks. Overall resilience did not differ significantly between the two groups directly post-intervention, nor 100 days later. However, positive coping, social integration, and family environment were improved after the TMV intervention.

Discussion

This study aimed to provide an overview of the studies conducted on PTG and resilience in AYA cancer patients. The included qualitative studies, showed that most AYA cancer patients have the capacity to be resilient or showed some form of PTG. Cross-sectional cohort studies found no significant differences in PTG and resilience between AYA cancer patients and healthy controls, except for two studies showing that (on-treatment) patients had lower levels compared to healthy controls. Sociodemographic and clinical characteristics were not associated with PTG or resilience, except for race. Social support was positively and enduring distress negatively correlated with PTG. Symptom distress and defensive coping were negatively and adaptive cognitive coping was positively associated with resilience. PTG and resilience were found to be of significant influence on general and health-related life satisfaction and HRQoL of AYA cancer patients. The two resilience interventions did not result in significant improvements in overall resilience levels of AYA cancer patients.

Prevalence of PTG and resilience: theoretical considerations

Overall, the results of the qualitative and quantitative studies suggest that AYAs with cancer experience at least some degree of PTG and resilience. This is in line with a study showing that almost 85% of childhood cancer survivors report at least one positive aspect of their cancer journey,[45] and another study showing that up to 87% of the adult cancer survivors report PTG.[46] The studies included in our review found no or only small differences in PTG and resilience scores between AYA cancer patients and healthy controls. However, prevalence rates of PTG or resilience are difficult to determine because of the heterogeneity of the study samples. The interpretation of these results is further complicated by the fact that for both, PTG and resilience, different definitions, theoretical frameworks and assessment tools were used.[47, 48] Most researchers adopted the model of Tedeschi and Calhoun[38] for analyzing PTG in the aftermath of cancer and relied on the associated PTGI assessment tool. However, this tool was derived from research on war, natural disasters or other types trauma and not cancer.[48] The extent of PTG experienced might be affected by the nature of the trauma.[49] Cancer is different compared to other traumas in terms of the internal nature of the crisis, the multiple stressors, and future-focused fears.[50] Cancer often has a nuanced onset (routine screening examinations), continues through cancer diagnosis and treatments, and it goes on for many years with the fear of future recurrences or disease progression. The PTGI does not assess the specific nature of the cancer experience. AYA cancer patients and healthy controls may have different reference points and are therefore not easily comparable.

With regard to resilience three general ways have been used to describe it: as a baseline characteristic, as an outcome itself or as a mechanism to improve (positive) outcomes.[51] Among AYAs with cancer, resilience is described as the process of finding or developing resources to manage stressors and reach positive outcomes,[10] and the two most commonly used frameworks are the Resilience in Illness Model[52] and its adolescent version.[10] This framework comprises of health-protective (e.g. social integration and courageous coping) and risk factors (e.g. illness related distress and defensive coping) and outcomes. Future research should explore the best framework for studying resilience and an assessment tool should be developed that assesses all components of resilience.

In addition, future research should focus on examining the relation between PTG and resilience, because this could have important implications for both preventive interventions as well as trauma counseling.

Correlates of PTG and resilience

PTG and resilience may not occur in all AYA cancer patients, identification of correlates creates opportunities to improve these outcomes. Sociodemographic and clinical factors were not associated with both outcomes. However, one of the included studies in our review found a difference between in-treatment AYA cancer patients who had lower PTG scores compared to both off-treatment AYA cancer patients and healthy controls,[35] which is congruent with studies among adult cancer survivors.[20] According to the Tedeschi and Calhoun definition, PTG needs time to appear in the aftermath of a traumatic event. It implies that moving beyond the daily demands of cancer and threat to one’s health or life provides room for greater processing of growth. Other cancer and treatment characteristics show contradictory associations with PTG and resilience among pediatric and adult cancer survivors.[6, 7, 20, 53, 54] In case of PTG this is not unexpected, as the PTGI, the most commonly used PTG assessment tool, does not explicitly refer to the medical nature of trauma and may therefore not be completely adequate to capture the full spectrum of positive reactions in cancer.[48] With regard to the sociodemographic variables, most studies showed no relationship between gender and positive outcomes in adults with cancer, although there is also evidence that women report higher levels of PTG.[20, 55, 56] There is some evidence indicating that racial or ethnic minority groups tend to report higher levels of PTG.[20] Several studies observed higher socioeconomic status (income and educational level) was associated with higher PTG or resilience,[57-60] however other studies found no relationship.[20] The choice of one or another questionnaire may have conditioned the emergence of specific variables that better fitted with the tool itself, resulting in a relevant risk of outcome bias.[48] More studies, using an appropriate definition, theoretical framework and assessment tool, must be conducted to identify sociodemographic and clinical correlates of PTG and resilience.

Psychosocial factors were more often found to be correlates of PTG and resilience. An adaptive coping strategy (cognitive or problem-oriented coping) was associated with higher levels of resilience among AYA cancer patients. This coping mechanism is used for protection of self in new dangerous situations, till sufficient resources are available for developing context-specific adaptive coping skills. Adaptive coping strategies such as acceptance, religious coping, and positive reinterpretation were also positively associated with PTG in adult cancer patient studies.[53, 54, 61, 62] Nonadaptive ways of coping (e.g. defensive coping) can be changed into adaptive coping if the AYA cancer patient has enough time to mobilize or create other protective factors to diminish the impact of cancer and its treatment. In their relatively short lives, most AYA cancer patients may not have experienced many major life events. As such, their coping skills to handle new traumatic situations may not have been optimally developed yet, which makes AYAs in more need of some support with coping.

Social support was positively correlated with PTG. Social support including acceptance and empathic conversations may strengthen AYA cancer patients to process their trauma, facilitate coping and increase adjustment.[63, 64] Ongoing support encourages AYA cancer patients to communicate openly about and cognitively process their cancer through self-disclosure.[8] Nevertheless, AYA cancer patients often indicate problems with maintaining normal, pre-cancer relationships with family and friends, informing others about their disease, maintaining school and/or work and other activities, and dealing with feeling different.[10] Studies have shown that support received from other AYA cancer patients is incredibly important for this age group.[63] Ways to enhance social support should be explored, although (online) peer support groups and age-specific information portals for AYA cancer patients have been shown to significantly reduce feelings of social isolation, improve knowledge, self-efficacy, problem-solving skills and effective interpersonal interactions.[65]

Stress was negatively associated with PTG,[29] indicating that low levels of distress experienced after cancer treatment has ended can stimulate processing of the cancer experience, allowing growth. This finding, however, is incongruent with the PTG theory of Tedeschi and Calhoun[38] suggesting that traumatic events may serve as promotors for the development of PTG because stress facilitates peoples' cognitive process for rebuilding their views of themselves, their environment and their future.[8] A study among childhood cancer survivors indeed found a positive correlation between post-traumatic stress and PTG.[45] Another study included in this review found a curvilinear relationship between post-traumatic stress (re-experiencing) and PTG (new possibilities and personal strengths),[30] suggesting that there may be an optimal level of (post-traumatic) stress that strengthens PTG. When the post-traumatic stress levels increase beyond that point, a person may be overwhelmed by the stress, and adaptation and PTG may be negatively affected.[66] The results of this study indicate that re-experiencing may help to adapt psychologically. More research is needed to determine the threshold by which stress levels become too high to allow PTG to take place.

Interventions

Searching for potential ways to enhance PTG or resilience among AYA cancer patients is important, as the results of this review show that both are associated with better HRQoL and higher levels of satisfaction with life. Based on the correlates of PTG and resilience found in this review, coping mechanisms and/or social support are potential targets for intervention. Until now there are no interventions that are convincingly successful in promoting PTG or resilience among AYA cancer patients. However, both described resilience interventions were underpowered and participants were not screened for low resilience levels before the start of the intervention. Furthermore, both interventions were brief in nature which may be insufficient to learn and incorporate new skills. The PRISM intervention seems promising as the intervention is based on important correlates of positive outcomes: stress management and coping skills. Future studies with sufficient power should further explore the efficacy of this intervention, whereby social support also should also be considered as an important element.

Implications for practice and future research

As a result of the lack of one standard definition, theoretical framework, and assessment tool, for both PTG and resilience, research is still inconclusive in identifying correlates and mediators of PTG and resilience.

Development of future interventions should be informed by the specific needs and capacities of AYAs with cancer. Future studies should investigate whether PTG and resilience can simply be encouraged by prompting AYA cancer patients to describe positive experiences that have resulted from cancer. An intervention among adult breast cancer survivors where survivors were asked to write about positive experiences (feelings and thoughts) related to their cancer, showed that those who wrote down positive feelings reported less health care professional visits and lower levels of distress than survivors who wrote down facts of their experience.[67] The correlates of PTG and resilience may inform researchers and health care professionals on key elements to target in future interventions. For example, health care professionals may be able to recognize protective (social support) or risk factors (stress) and enable coping by supporting adaptive coping strategies. Health care professionals can also assist with problem solving, giving information in small amounts, listening, and showing empathy.[68] Among adult cancer patients, two cognitive-behavioral interventions, including elements of relaxation exercises, conflict resolution and emotional expression, and coping skills training had positive effects on PTG.[69, 70]

Limitations

This review has several limitations which should be mentioned. First, the small number of included studies and the heterogeneity of study samples and designs, makes it impossible to draw definitive conclusions about prevalence rates and correlates of both outcomes. In addition, different instruments were used to assess PTG or resilience, which could have resulted in contradictory study findings. There is a lack of a unifying description and therefore subsequent operationalization and measurement of both constructs. Researchers should explore the best ways to measure PTG and resilience and determine cut-off values for these instruments, making it easier to distinguish those who adjust well from those who could probably benefit from a PTG or resilience promoting intervention. The quality of the included studies was moderate to high (except for the qualitative studies). However, three shortcomings that need attention for future studies are the patient response rates under 75%, the small patient sample sizes and cross-sectional study designs.

To conclude, most AYA cancer patients report some degree of resilience or PTG. The factors associated with PTG and resilience found in this review, including stress, coping and social support, provide tentative insight to improve the effectiveness of interventions aimed at promoting these positive outcomes and potentially buffer more negative outcomes.

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Chapter 6

Empowerment in adolescents and young adults (AYAs) with cancer: relationship with health-related quality of life

Suzanne EJ Kaal, Olga Husson, Saskia van Duivenboden, Rosemarie Jansen, Eveliene Manten-Horst, Petra Servaes, Judith B Prins, Sanne W van den Berg, Winette TA van der Graaf

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Abstract

Background: The difficulties adolescents and young adults (AYAs) encounter during a cancer experience may result in a reduction or absence of empowerment. The aims of the current study were to assess levels of empowerment and associated (demographic, clinical or psychological) factors and examine the association between empowerment and health- related quality of life (HRQoL) among AYA patients with cancer

Methods: Patients aged 18 to 35 years at time of cancer diagnosis and who were seen by one of the members of the specialized multidisciplinary AYA team of the Radboud university medical center, were invited to complete questionnaires regarding empowerment, HRQoL, and sociodemographic, clinical and psychological characteristics (autonomy, coping, unmet social support needs and psychological distress).

Results: A total of 83 AYA patients completed the questionnaires. The mean age of participants at a diagnosis was 27.5 years. The vast majority had been treated with chemotherapy (86%), had more advanced stage of disease and had completed treatment at the time of participation (74%). The mean empowerment level was 154.1 (standard deviation, 17.8) with a range of 114 to 200. Multivariate analysis demonstratrd that the autonomy subscales of self awareness ($\beta = .35$), capacity for managing new situations ($\beta = .19$) and social support ($\beta = .35$) were found to be positively associated with empowerment. Coping difficulties ($\beta = -.19$) were found to be negatively associated with empowerment. Empowerment was independently associated with physical ($\beta = .31$), psychological ($\beta = .50$), social ($\beta = .39$), religious ($\beta = .33$) and total HRQoL ($\beta = .52$; all $P<.01$).

Conclusions: Low levels of empowerment were associated with low levels of autonomy and social support, female sex and coping difficulties among AYA patients with cancer. Recognizing these patients as candidates for empowerment interventions ultimately could help to improve HRQoL in late adolescence and young adulthood.

Introduction

Adolescents and young adults (AYAs), diagnosed with cancer at the age of 18 to 35 years, form a distinct group between pediatric and adult oncology[1]. Our definition of AYA (those aged 18-35 years) is based on the organization of the health care system in the Netherlands, in which there is a clear distinction between pediatric (ages birth-18 years) versus medical oncology. According to Barr and colleagues "there is broad agreement but less than unanimity that adolescence ranges from 15 to 19 years of age, resulting in young adulthood beginning at age 20 years". Therefore the age range of 18 to 35 years used herein appears to indicate late adolescence and young adulthood[2]. In the Netherlands approximately 2700 AYA patients are diagnosed with cancer annually - which is approximately 5 times the number of cases diagnosed in children a birth to 17 years[3]. In addition to differences in tumor biology, limited progress in survival, lower clinical trial participation rates, and insufficient awareness of cancer symptoms among patients and professionals, this group has distinctive psychosocial and supportive care needs compared with their younger and older counterparts[1]. Late adolescence and young adulthood is a period of complex development; for example, it is during this period that one creates one's own identity and body image, and establishes autonomy, responsibility and independence. A cancer diagnosis poses existential questions to AYA patients regarding their future, encompassing premature confrontation with mortality; changes in physical appearance; increased dependence on parents; potential loss of reproductive capacity; and disruptions in social life, education and employment due to treatment. These factors may have a negative impact on health-related quality of life (HRQoL)[4].

Empowerment is a factor that may be associated with HRQoL and has become a topical issue in cancer survivorship over recent years[5-10]. With its roots in community psychology, empowerment was originally defined as "the mechanism by which people, organizations, and communities gain mastery over their lives"[11]. The topical nature and the extensive (mis)use of empowerment in health care has led to a lack of clarity in regard to its definition and measurement[12]. For example, empowerment can be viewed as a process versus an outcome, and on an individual versus collective level[12-14]. For this current study, we used the construct of psychological empowerment of Zimmerman[15] that views empowerment as an outcome measure on the level of the individual patient: "psychological empowerment is a feeling of control, a critical awareness of one's environment and active engagement in it". In accordance with a recent review on measuring and defining empowerment in patients with cancer[16], Zimmerman states that empowerment reflects a broad construct and comprehends intrapersonal, interactional, and behavioral components[15]. The intrapersonal component refers to how people think about themselves and includes perceived control, self-efficacy, perceived competence and mastery. The interactional component refers to how people think about and relate to their social environment, and the behavioral component of empowerment relates to concrete behaviors of a person to change his or her situation (e.g. active coping, and participation in decision making) [14, 15].

Empowered AYA patients with cancer may be more likely to understand and participate in their own care by mobilizing resources and taking actions that can reduce distress, enhance strategies for dealing with cancer and improve HRQoL[5, 6]. In view of this knowledge, it is important to evaluate which sociodemographic (eg, sex), clinical (eg, treatment intent) and psychological (eg, loss of autonomy, coping difficulties, high levels of psychological distress, and unmet social support needs) factors are associated with low levels of empowerment among AYA patients with cancer. This also may help us to identify those patients who might benefit from additional support or interventions.

In summary, the objectives of the current study were to assess the: 1) levels and associated factors (demographic, clinical and psychological) of empowerment; 2) association between empowerment and HRQoL among AYA patients.

Methods

Participants

Patients aged 18 to 35 years at the time of cancer diagnosis, and who had been seen by at least 1 of the members of the AYA team of the Radboud University Medical Center in The Netherlands, were invited to participate in this study. The AYA team is a dedicated multidisciplinary team including a medical oncologist, clinical nurse specialist, medical psychologist, and social worker. Patients consulting the AYA team receive regular medical care from their own treating medical specialist in the Radboud University Medical Center (medical oncologist, hematologist, surgeon, gynecologist etc.) and visit the AYA team for age-specific questions and care needs. In general, patients visiting the AYA team represent a group of patients with high disease severity, who are diagnosed with a relatively advanced stage of disease and undergoing intensive treatments, and who are reporting more difficulties with coping. Patients with lower stage disease (eg, cervical cancer, melanoma) who are treated solely by surgery, are not often seen by the AYA team.

For the current study, AYA patients with cancer were included independently of the status of treatment (during or after treatment), the type of treatment (surgery, chemotherapy, radiotherapy, immunotherapy/targeted therapy and hormonal therapy or a combination), or the number of AYA team visits (some patients only had one introduction talk with 1 of the members of the team and did not receive specific care thereafter) to depict the real-life heterogeneous sample of AYA patients with cancer visiting the AYA team. Inclusion commenced January 2012 and ended March 2016.

Procedure

Potential study participants were recruited via letters describing the study and inviting patients to participate in the study. Patients who were willing to participate had to actively opt-in to the study by providing written informed consent by email to a member of the AYA team. Participants were then sent a single set of questionnaires by email that could be completed online. The study was deemed exempt from full review and approval by a research ethics comittee (CMO Regio Arnhem - Nijmegen).

Measures

Empowerment

The Cancer Empowerment Questionnaire (CEQ) is based on Zimmerman's theory of psychological empowerment and to the best of our knowledge is one of first empowerment questionnaires validated in patients with cancer[8, 15, 16]. Validation in survivors of breast cancer provided a 4-factor structure representing the intrapersonal and interpersonal strengths of patients with cancer [8]. The CEQ consists of 40 items with 4 subscales: Personal Strength (19 items, range 19-95, α = .90), Social Support (9 items, range 9-45, α = .76), Community (6 items, range 6-30, α = .81) and Health Care (6 items, range 6-30, α = .78). Personal Strength encompasses intrapersonal aspects of empowerment regarding self-efficacy, self-esteem, optimism and personal competence. The remaining 3 subscales represent the interpersonal aspects of empowerment with items of perceived support from individuals close to the patient (Social Support), feelings of acceptance and support from the social community (Community), and the perception of good and collaborative relationships with health care professionals (Health Care). Examples of questions regarding each subscale are: “I think I am worthwhile” (Personal Strength), “The people around me accept me” (Social Support), “The society respects my rights as a citizen” (Community), and “My health care professionals are there when I need them” (Health Care). The 40 items are rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Total scores (scale) can rfeaenlgineg fsr oomf e4mo pto w2oeorm. Setnrto nagree ri ndicated by higher scores [8]. Baseline internal consistency was good (Cronbach’s α, .93).

Health-related Quality of life

The Quality of Life for Cancer Survivors (QoL-CS) questionnaire measures the HRQoL of patients with cancer. It consists of 41 items on the physical, psychological, social and religious impact of cancer on the life of the patient. Respondents rate themselves along an interval rating scale ranging from 0 to 10 for each item. For subscale scoring purposes, all items were ordered, so that 0 indicated the lowest or worst possible HRQoL, and 10 indicated the highest or best possible HRQoL outcome. An overall QoL score was computed by averaging all 41 items[17].

Associated factors

Sociodemographic and clinical characteristics

Demographic data, including age, sex, partnership, having children, living situation, educational level, and employment status were gathered by self-report. Medical data, including tumor type, disease stage, type(s) of treatment(s) received, treatment status (on/off treatment) and time since initial diagnosis were extracted from the patients’ medical records by 2 of the researchers [SK,SvD].

Autonomy-connectedness

The Autonomy Connectedness Scale (ACS-30) questionnaire measures individual differences in autonomy-connectedness (ie, the capacity for self-governance, including in social relationships). It consists of 30 items divided into 3 subscales: Self-Awareness (7 items, [eg, “I often do not know what my opinion is”]), Sensitivity to Others (17 items [eg, “I often wonder what other people think of me”]), and Capacity for Managing New Situations (6 items [eg, “I quickly feel at ease in new situations”]). All items are measured with 5-point scales, ranging from disagree to agree[18, 19]. Internal consistency in this study was good with α values of .81, .82 and .80, respectively.

Psychological distress

Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS), with 7 items each for assessing symptoms of anxiety and depression. All items were scored on a 0-point to 3-point scale, with higher scores indicating more symptoms. A total score was calculated, with higher scores indicating more distress[20].

Social support and coping

Two items (amount of social support and coping difficulties) were added as separate correlates for empowerment. They were selected from the QoL-CS questionnaire[17]. The question regarding the amount of social support was: “Was the amount of support you received from others sufficient?” For coping difficulties the question was: “How difficult is it for you nowadays to cope with the effects of disease and treatment?”. Respondents rate themselves along an interval rating scale ranging from 0 to 10 for each item. For social support a higher score indicates sufficient social support, whereas a higher score on coping indicates more coping difficulties.

Statistical analysis

Analyses were performed using Statistical Package for the Social Sciences version 22 (SPSS), Chicago, IL, USA and 2-sided P values <.05 were considered statistically significant. Descriptive statistics and frequencies concerning socio-demographic, clinical data, levels of empowerment and correlates were calculated. Pearson and Phi correlations were calculated to examine associations between 2 continuous variables and continuous and dichotomous variables, respectively. This first was performed for correlates of levels of empowerment and thereafter this was performed for correlates of HRQoL. To determine independent effects of covariates on levels of empowerment and HRQoL respectively, multivariate linear regression analyses were performed including only those covariates that were significant at the bivariate level.

Results

Sociodemographic and clinical patient characteristics

In total, 309 letters requesting participation in the study were sent to AYA patients with cancer visiting 1 of the members of the AYA team. A total of 89 patients, comprising 57% who opted to take part in the study (155 patients) and 29% of those invited (309 patients), completed the online questionnaire.

Six patients were excluded due to age criteria: 4 diagnosed with cancer at age <18 years and 2 were aged >35 years at the time of diagnosis. Table 1 shows sociodemographic, disease and treatmentrelated characteristics of the final sample (83 patients). The mean age at diagnosis was 27.5 years (standard deviation [SD], 4.6 years) with a range of 18 to 35 years and a median age at diagnosis of 27 years. Three patients (3.6%) were aged 18 and 19 years. The average time since diagnosis was 2.1 years (SD, 2.6 years) and 86% received curative treatment. Of the participants 52% were male. The most commonly diagnosed cancers were testicular cancer (34%) and sarcoma (19%).

Table 1: Characteristics of the AYA patient study sample

	Total N=83(%)
Gender	
Male	43(52%)
Female	40(48%)
Age at diagnosis M(SD), y	27.5(4.6)
Age at survey M(SD), y	29.6(4.8)
Time since cancer diagnosis M(SD), y	2.1(2.6)
Cancer diagnosis	
Testicular cancer	28(34%)
Sarcoma	16(19%)
Breast cancer	10(12%)
Lymphoma/Leukemia	10(12%)
Gynecological cancer	9(11%)
Melanoma	3(4%)
Other*	7(8%)
AJCC TNM Staging system stage of disease	
NA	9(11%)
Stage I	11(13%)
Stage II	25(30%)
Stage III	13(16%)
Stage IV	18(22%)
Unknown	7(8%)
Treatment intention	
Curative	71(86%)
Palliative	12(14%)
Treatment status	
Active	22 (26%)
Completed	61 (74%)

Table 1: Continued

Treatment type(yes)	
Surgery	70(84%)
Chemotherapy	72(87%)
Radiotherapy	24(29%)
Immunotherapy/targeted therapy	13(16%)
Hormonal therapy	7(8%)
Systemic therapy other	13(16%)
Partner	
Yes	58(70%)
No	24(29%)
Children	
Yes	27(33%)
No	55(66%)
Living situation	
With parents	14(17%)
On own	24(29%)
With partner	44(53%)
Highest completed education[a]	
Low/ Intermediate	38(46%)
High	44(53%)
Employed/studying	
Yes	68(82%)
No	15(18%)
Received social support meeting needs mean (SD)[b]	8.1(1.8)
Coping with effects of cancer and its treatment mean (SD)[c]	4.1(2.6)
Psychological distress mean (SD)[d]	11.0(6.6)
Autonomy connectedness mean (SD)	
Self-awareness[e]	25.9(6.1)
Sensitivity to others[f]	57.2(10)
Handle new situations[g]	19.2(5.5)

Abbreviations: AYA, adolescents and young adults; NA, not applicable; SD, standard deviation. Not all numbers add up to 83 because of missing data

* brain tumor in 1 patient, sigmoid carcinoma in 1 patient, orofaryngeal cancer in 1 patient, neuroendocrine tumor in 1 patiënt, salivary gland in 1 patiënt, adrenal carcinoma in 1 patiënt, and lung cancer in 1 patient.

[a] 0 indicates low/intermediate vocational education or less and 1 indicates high-level vocational education/university.

[b] Score ranges from 0 to 10, with a higher score indicating more social support.

[c] Score ranges from 0 to 10, with a higher score indicating more coping difficulties.

[d] Score ranges from 0 to 42, with a higher score indicating more distress.

[e] Score ranges from 7 to 35,with a higher score indicating more self-awareness.

[f] Score ranges from 17 to 85, with a higher score indicatng more sensitivity to others.

[g] Score ranges from 6 to 30, with a higher score indicating easiness to handle new situations.

Levels of empowerment

Mean empowerment level was 154.1(SD, 17.8), with a range of 114 to 200. The mean scores for each domain were 74(SD, 9.8) for Personal Strength, 36.5 (SD, 4.1) for Social Support, 19.7 (SD, 4.6) for Community, and 23.9 (SD, 3.4) for Health Care.

Associated factors of empowerment

Factors associated with total empowerment and the 4 empowerment subscales are presented in Table 2. Female sex was found to be negatively associated with total empowerment and all empowerment subscales except Social Support. Employment and education were found to be positively associated with the empowerment subscale Personal Strength. Higher disease stage was positively associated with the subscale Social Support. Palliative treatment intent was found to be negatively associated with Personal Strength. With regard to autonomy, self-awareness and capacity to handle new situations were positively associated with total empowerment and all subscales except self-awareness and the empowerment Community subscale. On the autonomy subscale, sensitivity to others was found to be negatively associated with total empowerment and the empowerment Community subscale. Perception of social support showed a strong positive association with total empowerment and all empowerment subscales. Coping difficulties and psychological distress were negatively associated with total empowerment and all subscales except for the empowerment Community subscale.

In multivariate linear analysis, using total empowerment as outcome, and including univariate significant correlates (except for psychological distress which was highly correlated with coping [correlation coefficient of >0.8]), the results remained significant for self-awareness (β = .35; P<.01), new situations (β = .19; P=.05), coping difficulties (β =-.19; P=.04), and social support (β =.35; P<.01), but not sex (β =-.14; P=.11) or sensitivity to others (β =.08; P=.38).

Table 2: Associated factors of empowerment

	Personal strength	Social support	Community	Health care	Total
Sociodemographic and clinical					
Age diagnosis, y	-0.05	-0.10	-0.01	-0.16	-0.08
Gender: 0 for male and 1 for female	-0.26*	-0.21	-0.28*	-0.31**	-0.32**
Partner: 0 for yes and 1 for no	-0.21	-0.12	-0.13	-0.06	-0.19
Educational level[a]	0.20	0.09	-0.04	0.05	0.13
Living status[b]	-0.05	-0.03	-0.08	-0.09	-0.07
Work/school 0 for no and 1 for yes	0.22*	-0.03	-0.13	-0.02	0.07
Children 0 for no and 1 for yes	0.04	-0.01	-0.03	-0.09	-0.01
Time since diagnosis, y	0.07	-0.03	-0.18	0.03	-0.01
Disease stage[c]	-0.12	0.26*	0.11	0.17	0.01
Treatment status[d]	0.03	-0.12	-0.09	0.06	-0.02
Treatment intent[e]	-0.23*	-0.10	0.01	-0.08	-0.16
Chemotherapy 0 for no and 1 for yes	0.13	0.09	0.03	0.09	0.12
Autonony connectedness					
Self-awareness	0.55**	0.47**	0.19	0.27*	0.51*
Sensitivity to others	-0.21	-0.14	-0.24*	-0.07	-0.22*
Capacity new situations	0.51**	0.42**	0.23*	0.27*	0.48**
Other					
Amount social support meeting needs	0.34**	0.46**	0.39**	0.46**	0.48**
Coping difficulties	-0.47**	-0.23*	-0.11	-0.25*	-0.38**
Psychological distress	-0.66**	-0.48**	-0.16	-0.37**	-0.58**

*p<0.05;**p<0.01

[a] 0=indicates low/intermediate vocational education or less and 1 indicates highlevelvocational education / university.

[b] 0= indicates with parent and 1 indicates independent/together with partner(children) or friends.

[c] 0 indicates stages I and II, and 1 indicates stage III and IV.

[d] 0 indicates receiving treatment and 1 indicates completed treatment.

[e] 0 indicates curative and 1 indicates palliative.

Table 3: Correlations between empowerment, other covariates and health related quality of life (HRQoL)

	Physical	Psychological	Social	Religious	Total HRQoL
Empowerment					
Personal strength	0.45**	0.63**	0.42**	0.29**	0.65**
Social support	0.26*	0.43**	0.40**	0.22*	0.46**
Community	0.21	0.21	0.22*	0.24*	0.28*
Health care	0.41**	0.42**	0.45**	0.27*	0.52**
Total	0.44**	0.58**	0.47**	0.32**	0.63**
Sociodemographic and clinical					
Age diagnosis, y	-0.18	-0.11	0.01	-0.05	-0.12
Age survey, y	-0.13	-0.05	0.10	-0.05	-0.05
Sex: 0 for male and 1 for female	-0.35**	-0.39**	-0.35**	-0.16	-0.43**
Partner: 0 for yes and 1 for no	-0.11	-0.09	0.05	-0.15	-0.09
Educational level[a]	0.15	0.01	-0.18	0.15	0.03
Living status[b]	-0.01	-0.07	0.02	0.01	-0.03
Work/school: 0 for no and 1 for yes	0.22*	0.17	-0.09	0.37**	0.20
Children: 0 for no and 1 for yes	0.11	-0.04	0.04	-0.01	0.02
Time since diagnosis, y	0.04	0.03	0.11	0.02	0.06
Disease stage[c]	-0.11	-0.17	-0.04	-0.23	-0.19
Treatment status[d]	0.27*	0.16	0.04	0.10	0.18
Treatment intent[e]	-0.27*	-0.31**	-0.13	-0.30**	-0.35**
Chemotherapy: 0 for no and 1 for yes	0.14	0.18	0.10	-0.05	0.16
Autonomy-connectedness					
Self-awareness	0.14	0.20	0.25*	0.12	0.25*
Sensitivity to others	-0.01	-0.31**	-0.32**	0.07	-0.24*
Capacity new situations	0.31**	0.36**	0.25*	0.20	0.40**

*p<0.05;**p<0.01

[a] 0 indicates low/intermediate vocational education or less and 1 indicates high-level vocational education/university

[b] 0 indicates with parent and 1 indicates independent/together with partner (children) or friends.

[c] 0 indicates stages I and II and 1 indicates stage III ansd IV.

[d] 0 indicates receiving treatment and 1 indicates completed treatment.

[e] 0 indicates curative and 1 indicates palliative.

Associations between empowerment and HRQoL among AYA patients

Bivariate correlations demostrated that all empowerment subscales were positively associated with HRQoL, except for the Community subscale which was not associated with physical and psychological HRQoL. Several sociodemographic, clinical and personal factors were also found to be significantly associated with HRQoL(Table 3).

Female sex was negatively associated with all HRQoL subscales except for the religious subscale. Having work or attending school was positively associated with the religious HRQoL subscale. Completion of cancer treatment was positively associated with the physical HRQoL subscale. Palliative treatment intent was negatively associated with all HRQoL scales except the social subscale. The autonomy subscale of Self- Awareness was found to be positively associated with total and social HRQoL. The autonomy subscale demonstrated that sensitivity to others was negatively associated with psychological, social and total HRQoL. In addition, the autonomy subscale capacity to handle new situations had a strong positive association with all HRQoL scales except the religious subscale. To assess the independent association of empowerment with the 5 HRQoL scales, multivariate linear regression analyses were conducted with HRQoL scales as outcomes, total empowerment score as an independent variable, and including all significant correlates in univariate analyses. Empowerment remained significant for physical ($\beta = 0.31$; $P<.01$), psychological ($\beta = .50$; $P<.01$), social ($\beta = .39$; $P<.01$), religious ($\beta = .33$; $P<.01$) and total HRQoL ($\beta = .52$; $P<.01$).

Sensitivity analysis demonstrated that the empowerment scales were only significantly associated with HRQoL for those patients treated with curative intent and not for those treated with palliative intent.

Discussion

This resultsofthecurrentstudy indicate that AYA patientswithcancerwho were treated in a specialized care center had relatively high levels of empowerment. There was a wide range of levels of empowerment, indicating room for improvement. Empowerment levels in the current study were comparable to those in a previous study in patients with breast cancer; however, this study only included female patients who were older than patients in the current study sample[21]. The results of the current study demonstrated that the most important factors associated with empowerment in AYA patients were autonomy, sex, social support and coping. This provides beneficial insight into groups that may benefit from support interventions that aim to empower AYA patients. AYA patients with higher levels of empowerment were more likely to be male, have higher autonomy scores and receive more social support. These patients also reported fewer difficulties in coping and lower levels of psychological distress. The current study data have demonstrated the importance of high levels of empowerment because this was found to be was positively associated with HRQoL.

Autonomy was strongly associated with empowerment. Self-awareness and the capacity to handle new situations were independently associated with total empowerment. Developing autonomy is generally experienced as young people mature[22]. Although many AYA patients have developed decisionmaking skills regarding their own health or life goals[22], others will still look to others to help them with decision-making and indeed they may return to a state of dependency when faced with cancer[23]. Health related information should be delivered in a manner which is appropriate to the age of the patient because this is critical in helping AYA individuals learn to cope with their disease and navigate the health care system[24]. The capacity to handle new situations is closely related to the concept of coping. In their relatively short lives, most AYA patients have not encountered many major life events. AYA patients may require more support as they have not had the opportunity to develop skills that enable them to cope with new and challenging situations. We found that being female had a significant, negative correlation with empowerment. This may be explained by the findings of a study that demonstrated that women tend to use less effective, emotion-focused coping strategies, whereas men use more effective problem-focused or instrumental methods of handling stressful experiences[25]. Additional support for female AYA patients may be warranted; however, we should not assume that all male AYA patients will require less social support.

Although AYA patients often feel isolated, perceived social support from family and friends contributes to high levels of empowerment[7]. A cancer diagnosis and its treatment lead to increased dependency on parents and/ or partners and sets AYA patients apart from their healthy peers. AYA autonomy and the development of identity in general depends largely on peer acceptance and relationships[26]. Not unexpectedly, studies have shown that support from other AYA cancer patients is incredibly important for this age group in helping them to cope with their disease[27]. In addition, AYA patients want to provide support to their own family and friends to create a sense of self-worth, however this contribution is not always possible during their disease trajectory due to the effects of cancer and its treatment[28]. Those with high levels of sensitivity towards others, more commonly women, have greater difficulty accepting this realization and therefore feel less empowered[25]. As the results of the current study demonstrate, return into society, through employment or education, contributes further to empowerment by creating a sense of selfworth/ confidence and perceiving oneself as being useful. A perceived lack of social support, absence of self-worth and appropriate coping skills may all have a negative effect on psychological distress, which itself was a strong negative correlate of empowerment. Last, the results of the current study demonstrate that treatment intent (curative vs. palliative) also contributes to the levels of personal strength. The needs of AYA patients with advanced cancer intensify as they near the end of their lives[29]. The physical changes associated with advanced disease result in loss of capacity to manage activities of daily living and aspects of medical regimens[5]. In addition, the stress of living with an enduring sense of loss brings new challenges, such as when to hand responsibilities to others and whether to discuss emotional or spiritual concerns and end-of life decisions. Providing appropriate support to allow patients to maintain a level of autonomy is very important in this phase[5].

Given the strong correlation between empowerment and HRQoL found in the current study and others[30] and relatively high levels of empowerment measured in this AYA sample, strategies to reinforce empowerment in AYA patients should be explored. Interventions could focus on 1 or all 4 domains of empowerment. First, the sense of personal strength can be positively influenced by self-management (ie, the comprehensive engagement of the AYA patient in problem-solving, decision-making, and daily health-related behaviors in partnership with health care professionals and community)[31]. Self-management will help patients to manage the medical aspects of cancer, by managing life roles (including changes in roles brought by cancer), and managing the psychosocial consequences of cancer[32]. Such a selfmanagement intervention might include cognitive behavioral therapy components such as psychoeducation, cognitive reframing, goal planning and process evaluation[33]. Second, social support can be enhanced by offering reallife and digital platforms for AYA patients in which they can virtually meet and share information and feelings with peers[34]. For example, online peer support groups and age-specific information portals for AYA patients have been shown to significantly reduce feelings of social isolation, improve knowledge, selfefficacy, problem-solving skills and effective interpersonal interactions[35]. With regard to the third empowerment dimension, community, attention should be paid to reframing the perception of AYA patients as a burden to society. The fourth empowerment dimension, health care, can be improved by creating inpatient and outpatient dedicated multifunctional spaces to suit the needs of AYA patients, training AYAdedicated professional caregivers and establishing educational programs for healthcare professionals. For example, additional medical training in fertility preservation or AYA survivorship care could be provided at the (under)graduate level, in primary care residencies, and adult oncology fellowships. Future research should explore the best ways to increase levels of empowerment among AYA patients.

The current study has several limitations. First, all participants were treated in a single center and received multidisciplinary care by a dedicated AYA team. Therefore, it could be that the empowerment levels of the current sample are higher than those of AYA patients treated in other centers in The Netherlands without age-specific care. However, the patients in the current study sample were diagnosed with a relatively advanced stage of disease and were treated intensively, mostly with > 1 treatment modality. This might be an overestimation in disease severity of the entire AYA cancer population, in which lower stage disease (cervical cancer, melanoma, thyroid cancer, and brain tumor) treated solely by surgery is more common. Both factors limit the generalizability of the results of the current study. A second limitation of the current study is the low response rate, which is not unusual in studies in young patients with cancer but was even lower than in previous questionnaire studies[36, 37] among AYA patients (29% response rate in the current study sample vs 43% and 52% in previous studies). Unfortunately, we do not have information regarding the reasons for no participation. Because demographic data were not collected of the nonresponders, we could not rule out selection bias. Third, empowerment is rarely formally assessed as outcome and to our knowledge a few validated questionnaires exist, particularly for the cancer setting[6], therefore making it difficult to compare the results of the current study with those from other groups of cancer patients. Fourth, the cross-sectional design of the current study limits the determination of causal associations between the study variables. Longitudinal research is needed to assess changes in empowerment levels over time to determine the best time to intervene for those patients with low levels. Fifth, the question remains whether the higher levels of empowerment are caused by the fact that all AYA patients consulted at least 1 member of the multidisciplinary AYA team, or by the psychometric properties of the empowerment questionnaire. Although the CEQ has demonstrated good psychometric properties, to the best of our knowledge the sensitivity and specificity of this instrument have not been tested and there is no validated cutoff point in the cancer setting.

Empowerment is an important factor related to HRQoL in late adolescence and young adulthood. Empowerment levels as measured in the current study were quite high in AYA patients with cancer who were treated in a specialized care center. Low levels of empowerment were associated with low levels of autonomy and social support, female sex, and coping difficulties. Future research should explore the best ways to increase empowerment in identified risk groups.

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Chapter 7

Online support community for adolescents and young adults (AYAs) with cancer: user statistics, evaluation and content analysis

Suzanne EJ Kaal, Olga Husson, Fleur van Dartel, Karin Hermans, Rosemarie Jansen, Eveliene Manten-Horst, Petra Servaes, Tom H van de Belt, Lucien JLPG Engelen, Judith B Prins, Suzan Verberne, Winette TA van der Graaf

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Abstract

Purpose: Peer support is an important unmet need among adolescent and young adult (AYA) cancer patients. The aim of this study is to describe the use and evaluation of a Dutch secure online support community for AYA diagnosed with cancer between 18 and 35 years.

Methods: User statistics were collected with Google analytics. Community members were asked to complete questionnaires on the usefulness of the community. A content analysis using Linguistic Inquiry and Word Count was performed.

Results: Between 2010 and 2017, 433 AYA became a member of the community (71% female; mean age at diagnosis 25.7 years; 52 Dutch hospitals represented). The mean time since diagnosis when subscribing to the community was 2.7 years (SD 4.4). Questionnaire data among 30 AYA community members indicated that the use of the community resulted in acknowledgement and advice regarding problems (56%) and the feeling of being supported (63%). Almost half of the respondents felt less lonely, 78% experienced recognition in stories of other AYA. Anonymized content analysis (n=14) showed that the majority of the online discussions encompassed emotional and cognitive expressions, and emotional support.

Conclusion: The secure Dutch online AYA community can help AYA cancer patients to express feelings, exchange information, address peer support and has been found helpful in coping with cancer. As AYA cancer patients often lack the option to meet each other in person the AYA community is helpful in establishing peer support. Its use would benefit from promotion by health care professionals.

Introduction

Adolescence and young adulthood are crucial phases regarding social, professional, physical and psychological development. Having cancer seriously disrupts this development and can have a negative impact on issues regarding control over life, body image, finances, education, work plans, relationships and plans for having children.[1] The Dutch definition of AYA (diagnosed with cancer between 18 and 35 years) is based on the organization of the health care system in the Netherlands, in which pediatric oncology, for patients between 0 and 18 years at diagnosis is centralized, and adult oncology is only centralized for rare or complex cancer types. AYA cancer patients can not profit from integrated care provided by pediatric oncology centers.

AYA cancer patients frequently (40-50%) report unmet (supportive) needs including contact with peers, access to age-appropriate information, treatment facilities, emotional support services and fertility services,[2-4] thus underlining the fact that supportive care for this age group is not optimal to address all age-specific needs.[5] In response, in the Netherlands and other European countries initiatives to improve AYA cancer care have started recently.[6,7]

E-Health interventions are increasingly being used in cancer care, e.g. to support patients in managing problems in daily life and gaining knowledge.[8] E-Health can be defined as "information and communication technology, especially the Internet, to improve or enable health and health care".[9] According to the behavior change model of Ritterband, internet interventions can lead to symptom improvement through a combination of personal and environmental factors on the one hand (e.g. knowledge, motivation and beliefs) and specific website characteristics on the other hand (e.g. appearance, content, delivery).[10] The internet can be used by patients to find (medical) information and share stories on weblogs, forums, and online social networks (Facebook, Twitter) and online communities.[11] Online communities are platforms where individuals meet and exchange experience and information.[12] Previous studies showed that participating in an online community can have an empowering and therapeutic effect: patients find informational and emotional support,[13,14] recognition,[12,15] emotional expression, and insight.[16] As a technical- and electronics-savvy generation, AYAs are primed to benefit from supportive care delivered through e-Health, alongside usual care.[17,18] Currently there are six AYA communities/websites with different features to exchange informational, emotional and social support as described in Table 1. However, none of them provides a secure environment.

Table 1: Existing online communities/digital support services for AYA/TYA cancer patients worldwide

Author, year, country	Type of community /online support group	Sample (N)	Age range (years)	Goal study	Means	Main results/conclusion
Love 2012 [19] Crook 2017[29] Thompson 2015[30] Donovan 2014[32] Pounders 2017[31] Texas, USA	Online AYA cancer community, anonymous	6000 plus users (+ small proportion of family, friends and professionals)	15-39	- Content analysis of 350 randomly sampled messages - Examine challenges of online support - Difference in language between online and offline support groups - Gain insight into the patterns of social support in response to AYAs' expressions of uncertainty - Better understand gender and identity issues among female AYA	- Data analysis of 'speech events' - Qualitative coding of transcripts of messages - Linguistic Inquiry and Word Count of transcripts - Analysis of 510 responses to posts - Analyzing individual message blog posts with text-mining software	- Exchange support, coping with emotions, describe experiences, enact identity and communicate membership - Challenges regarding soliciting support, disclosing to a community, advocacy online, negative sentiment evaluating health care services and asynchronous communication. - Differences between online and face-to-face support groups in terms of content and style words - 67% of posts contains multiple types of support - Female AYA experience issues pertaining to infertility, feeling like a bad mom, hair loss, scarring, dating, and intimacy.
Fasciano 2015[35], Boston, USA	Website with social networking capacity	N= 30 YA's completed online survey (of 188 registered)	18-39	Development and content of YA- website	Survey among users about use, satisfaction, emotional well-being	Website is helpful, particularly in social networking function. YA's experienced increased connection with others. Some YA's experienced increased distress
Gaulin 2010[43], USA	'Group Loop' American online community	NM	Adolescents	Assess impact of discussion boards and online support groups as a self-help tool for supporting the coping skills	Analysis of messages	- Exchange peer support and information about treatment. - Facilitators helped them to cope
Elwell 2011[44], USA	Computer-mediated support group (no subscription or registration)	NM	Adolescents	Explore types of social support using a qualitative approach.	Thematic analysis of 393 messages	- Exchange informational, emotional and social support - Useful with and without facilitator

Table 1: Continued

Griffiths 2015[34], UK	Realshare online support community	12	16-30	Describe development and evaluation Realshare online community	Focus-groups	- Helpful in communication and exchanging support with other patients and to arrange face-to-face meetings - A facilitator can be beneficial to encourage user interaction
Patterson 2014[33], Australia	Canteen online and phone mental health support service	NA	12-25 (young people living with cancer)	NA	NA	- Find information, connect with others, express feelings, utilize tools for support, access to professional psychosocial support - Service available for patients and offspring and siblings of family members with cancer

AYA = adolescent and young adult
YA = young adult
NM = not mentioned
NA = not applicable
TYA: teenager and young adult

Because AYA with cancer express age-specific peer support as an important unmet need and exchange of information can be rather privacy-sensitive, a secure, closed online community could be an asset addressing this need.[18-20] In 2010 an online community named AYA4 (All Information You've Asked for) was developed by and for Dutch AYA cancer patients treated at the Radboud university medical center (Radboudumc). This online community became available for all AYA cancer patients in the Netherlands in 2014. The aim of this article is to describe how the Dutch online AYA community is currently being used and to evaluate in particular (1) user statistics (2) usefulness and (3) content analysis addressing the psychological processes expressed in the messages on the forum.

Methods

Development of an online AYA community

The online community for AYA cancer patients was developed in close collaboration between the department of medical oncology, REshape & Innovation Center and AYA cancer patients of the Radboudumc. The community works as follows. At first access a community manager verifies age and disease specific information in the treating hospital. A disclaimer explains details of the community, for example that members have to sign a digital will to define what has to be done with their community content after one's death. The content of the community is only accessible for AYA patients with login details. The only person who has access and is able to communicate with all users is the community manager, a non-health care professional, trained in communication, who is online for about four hours daily (with a stand-in in case of absence). When patients log in for the first time, they are welcomed by the community manager and they are being notified that she can facilitate forum discussions. She will not share personal information of AYA community members with health care professionals, unless the AYA patients gives explicit permission to do so.

Procedure

The Ethics Committee of the Radboudumc judged that no detailed review was warranted given the non-intrusive character of this study (#2016-2872).

Study 1: User statistics

When signing up to the community, patients have to fill out the following information: first name, surname, gender, date of birth, telephone number, email address, treating hospital, patient identification number, treating physician, nurse specialist, type of cancer diagnosis, age at and date of cancer diagnosis, date of start treatment and what to do with the account in case of death. Logging data (assessed 11 April 2017) about activity and duration of logging in were analyzed using Google Analytics, a web analytics service offered by Google, that tracks and records website traffic. Login data of the community manager were excluded from this analysis.

Study 2: Evaluation

The evaluation study of the online AYA community was part of a larger as yet unpublished study aimed to gain insight into the supportive care needs of AYA cancer patients in the Netherlands. Patients aged between 18 and 35 years at time of cancer diagnosis were invited to participate and were recruited via a website of patients advocates (www.kanker.nl and www.aya4net.nl). Participants (n=66) were asked whether they were familiar with AYA care and if they were aware of the existence of the online AYA community. 59% (n=39) indicated to know the community. Nine of them were not a member of the community and were asked for their reasons of not being a member. Those patients who indicated to be a member of the community (n=30) were asked to answer questions about the usefulness of the community.

Study 3: Content analysis

The content of the forum (discussions between AYA patients) contains privacy-sensitive personal information: names, diagnoses, and shared experiences. This type of information cannot be used for research purposes without the explicit consent of the authors, in this case the AYA patients.[21] Therefore, we asked the members permission to use the content of their forum messages through an opt-in procedure: we published a message on the forum in the first half of April 2016 in which we explained the aim of our study and asked the users to give consent for using their data in anonymized form. The data of patients who gave informed consent were anonymized according to recommendations of King.[22] An independent research assistant went through all messages in our sample manually and replaced all mentions of person names (except for names of caregivers) by the string '****'. All anonymized messages by users who gave consent were brought together in a sample that we will refer to as the anonymized sample.

A commonly used and well-studied methodology for investigating the psychological processes through language use is the Linguistic Inquiry and Word count (LIWC).[23] LIWC analyzes texts for indicators of psychological processes that are important for psychologically processing of difficult experiences.[24,25] The developers of the LIWC defined a set of linguistic and psychological categories that can be recognized by words in the text. For each category, they defined a set of words that are indicators for that category. For example, the word *me* is an indicator of the linguistic category '1st person singular', and the word *good* is an indicator of the psychological category 'positive emotions'. We used the Dutch version of the LIWC consisting of 66 categories.[26] There are five types of categories: (1) standard linguistic dimensions (e.g. personal pronouns, 1st person singular, past tense verbs); (2) psychological processes (e.g. positive emotions, anxiety, humans); (3) relativity (time and space); (4) personal concerns (e.g. work, money, religion); (5) experimental dimensions (swearing). The categories are organized hierarchically. For example, the main category 'cognitive processes' under 'psychological processes' has several subcategories, among which 'insight', 'inclusive', and 'exclusive'. Due to this hierarchy, a word can belong to more than one category. For example, the word *ik* ('I') occurs in the category 'pronoun' as well as the category '1st person singular'.

The LIWC has been used before to distill these psychological processes from the content of online support communities.[27,28] In this study, we did not analyze the language use of individual authors on the forum, but quantified the presence of LIWC categories in the anonymized sample as a whole. We implemented the LIWC using the word lists published for the Dutch version of the LIWC.[26] Our LIWC script takes as input the complete text of our anonymized sample, and a dictionary of LIWC categories with the indicator words per category. The script splits the text in words, then looks up each word in the LIWC dictionary, and adds a count for the corresponding LIWC category. For example, each occurrence of the word *me* in the forum leads to a count for the category '1st person singular' and each occurrence of the word *good* in the forum leads to a count for the category 'positive emotions' The output of the script is a count of indicator words occurring for each LIWC category. We sorted the categories by their frequencies of occurrence in order to analyze which linguistic and psychological categories are the most frequent in the forum. Results are depicted as relative word counts per category, which is the sum of the numbers of occurrences of all the words in the category divided by the total number of words in the sample.

Results

User statistics

As of November 2017 the community has 433 registered members with a mean age at diagnosis of 25.7 years (SD 4.9) of which 71% is female. Of these members 18% were diagnosed with breast cancer, 17% with lymphoma, 10% with sarcoma, 7% with leukemia and 7% with testicular cancer and 41 % with other cancer types. The mean time since diagnosis when subscribing to the online AYA community was 2.7 years (SD 4.4) with a median time of 1 year. Members were from 52 out of 91 hospitals in the Netherlands. In 2016 the online AYA community was visited 35,327 times. A visit is defined as a single online activity of a person at a certain time point by means of an electronic device. On average a visitor was online for 1 minute and 23 seconds and looked at 2.47 pages per visit. The most frequently visited part of the community is the introduction page where AYA cancer patients introduce themselves by giving background information about their diagnosis, treatment trajectory and daily life problems because of cancer.

Evaluation

Sixty-six patients answered AYA questionnaires of whom 39 (59%) responded to have been informed about the AYA community. Thirty of them (77%) became member of the AYA community and used the community on a regular basis. The nine patients who were not a member indicated that they had no interest (3 patients), thought it was not useful for them (1 patient), indicated that the community was not available at the time they were diagnosed (2 patients), or were too fearful to hear the stories of other patients (3 patients). Of the 30 community members, 25 (83%) were female. Of this group, mean age at diagnosis was 25.6 years (SD 6.4, range 18-35) and mean age of questionnaire completion was 29.8 years (SD 5.3, range 22-39). Most frequent cancer diagnoses were breast cancer (20%), lymphoma (17%) and brain tumor (10%). Nine (30%) members rated the community as a little bit useful and 18 (60%) rated the community as highly useful, 3 (10%) patients had no opinion. Use of the community resulted in acknowledgement of their problems (56%) and the feeling of being supported and having valuable contacts with peers (63%). Almost half of the users felt less lonely, 78% experienced recognition in the cancer stories of other AYAs. In an open question AYA patients indicated the strong willingness to do something for other patients as a main reason to be an active member of the community (Table 2).

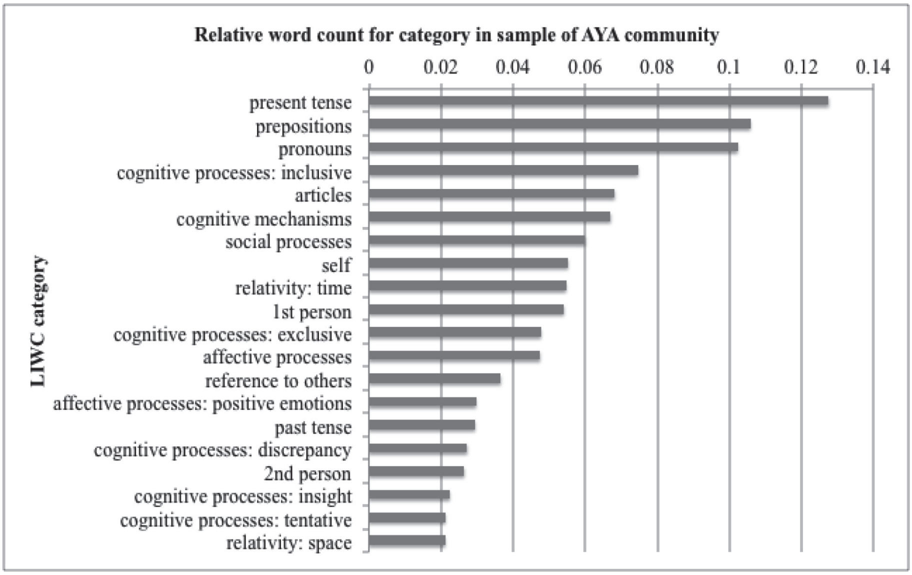
Table 2: Answers to the evaluation questionnaire about usefulness of the online AYA community among 30 members

Answers given about usefulness community	AYA community members (%)
I feel listened to	9 (33%)
I get recognition/acknowledgement	15 (56%)
I find recognition in the stories of peers	21 (78%)
I don't feel lonely any more	13 (48%)
I have good contact with peers	17 (63%)
My questions are being answered	9 (33%)
I feel more self-confident	7 (26%)
I get advice about coping with problems	12 (44%)
I make new friends	12 (44%)
I feel reassured	4 (15%)
I feel safe	7 (26%)
I feel supported	17 (63%)
Other	- It gives me the opportunity to share knowledge and to help others. It appears valuable to do something in a hopeless situation - I can support others - It is good to notice that I am not the only person with problems

Content analysis using LIWC

Only 14 members of the online community provided consent for use of their message in our content analysis. Together, these 14 members have posted 1896 messages on 293 topics between February 2014 (date online AYA community became available as national service) and June 2016. This is 44% (total amount of messages was 4332) of the total number of messages posted in this period, indicating that these 14 members are among the most active members of the forum. The mean number of messages posted by the included users is 135 (SD 103, range 5-386). We analyzed the 1896 messages in our sample using the LIWC categories. The total number of words in the sample is 108,881; the number of distinct words is 11,622. Of these, 1,981 occur in one or more LIWC categories. Figure 1 shows the 20 most frequent LIWC categories in the sample, with their relative word counts. The most frequent LIWC category is 'present tense'. There are 13,888 occurrences of words from that category in our sample (e.g. 'is', 'have', 'be', 'am'). This gives a relative word count of 0.128 (13,888/108,888) for the category 'present tense'.

Figure 1: The 20 most frequent LIWC categories in the online AYA community sample, with their relative word counts



LIWC: Linguistic Inquiry and Word Count
AYA: Adolescent and Young Adult

Discussion

This study reports about the use, evaluation and content analysis of the online community for Dutch AYA cancer patients. To our knowledge, this is one of the first secure, closed communities for AYA cancer patients in Europe. Our online community is only accessible for AYA patients and survivors which is in contrast with the large USA community where family, friends and professionals also have access.[19,29-32] The Australian community is also accessible for siblings and offspring of family members with cancer.[33] In the United Kingdom and Australia, digital platforms focus on younger age groups (16-25 years[34] and 12-24 years[33] respectively) in comparison to the USA online support forum who serves AYA cancer patients between 15 and 39 years. All online communities have in common that members provide and receive informational, emotional and/or social support to some degree.

User statistics of AYA communities were never reported. The user statistics of our study showed that the most common tumor types were breast cancer and lymphoma and that members were most often women. This is in line with previous research where most members were female.[34,35] It could be that men have less need for peer support and are therefore less likely to become a member, or prefer other kinds of peer support e.g. face-to-face or via sporting activities.[36] The short mean duration of online community visits may indicate that members use the community not as an extensive chat service but more as a forum to gain knowledge, express emotions and get recognition. However, it might also be an indication of the fact that AYA patients got scared of all that is written or that they did not like the online community and thought it was something else. In this way the results of the current study are hypothesis generating and further in depth research about the reasons for the short online duration time is recommended.

More than half of the members participating in our study rated the community as highly useful especially with regard to acknowledgement of feeling supported and establishment of valuable contacts with peers. This is in line with the results of the content analysis showing that members of the online AYA community indeed find emotional and cognitive expression, and emotional support. Given the theory of Ritterband, it could be hypothesized that higher levels of emotional and cognitive expression and emotional support may lead to better symptom control as this theory stated that internet interventions can lead to symptom improvement through mechanisms like social support, transferring knowledge and feelings of recognition.[10]

The interpretation of the LIWC categories displays that the first three categories in Figure 1 are standard linguistic dimensions. Personal pronouns and especially references to self (*I*, *me*, *mine*) are very common in discussion forum messages, indicating that the authors share narratives about themselves.[37] The most interesting categories in Figure 1 are the cognitive processes, the social processes and the affective processes. The category cognitive processes includes the subcategories 'inclusive', 'exclusive', 'discrepancy', 'insight' and 'tentative'. Examples of words that belong to the category 'inclusive' are: *also*, *with* and *completely*, while example words of the category 'exclusive' are: *without*, *outside* and *except*. The category discrepancy covers words such as *should, hope, must* and *want*, indicating a reality that is different than expected or wished for. The category 'insight' contains words such as *find, see*, and *know*, indicating insightful disclosure, a construct of empowerment that has been reported before for peer-directed patient support groups.[28] The category 'tentative' contains words such as *maybe*, *hope*, and *sometimes*, indicating uncertainty. The category social processes covers words that describe interactions such as *ask*, *people* and *welcome*, The category affective processes includes feelings and responses. In the online AYA community sample, positive emotions are the most prominent, with words such as *good*, *success*, *nice*, *happy*, and *better*. The high frequency of words indicating cognitive, social and affective processes may indicate that members of the online community find emotional support, emotional expression and insight on the discussion forum.

In 2012, Love *et al.* reported about content analysis of messages in an open online AYA cancer support forum in the USA. They found that AYAs exchange emotional and informational support, cope with difficult emotions, use particular language to describe experiences, enact identity, and communicate membership on this online cancer support forum.[19] Although we used another method to explore content, our results are largely in line with Love *et al*. In our study we also found that the majority of online discussions encompassed emotional support and emotional expression. Moreover, our results show that the community members gained more insight, expressed by words related to thinking, knowing and considering. A difference between both studies, is that our content analysis was based on larger amount of messages than in the study of Love *et al*.

The main limitation of our study was the low participation rate of AYA community members which may limit the generalizability of our results. This may be explained by several factors. First, although in the Netherlands every year approximately 2,700 patients between the age of 18-35 years are diagnosed with cancer, currently the AYA community has only 433 members. This might be attributable to the fact that patients and/or health care professionals are not familiar with AYA care and that the online AYA community only recently became available on a national level. Second, only a small part of the community members is active in discussions. This is in line with previous literature showing that only 10% of community members are active posters, the remaining 90% can be classified as 'lurkers'.[38] Third, as the online AYA community was developed eight years ago and patients grow older, some early members may now have less need for peer support. Fourth, interviews with AYA cancer patients also revealed that the online AYA community was used to establish a first contact with peers and afterwards other faster social media like WhatsApp were used to intensify the contact. Fifth, we cannot rule out selection bias, as patients recruited in the evaluation and the content analysis study might be the ones that are highly in need of peer support ('superusers') due to multiple health problems or are the patients who act as patient advocates.

The online AYA community is an example of an e-Health intervention, that is highly valued by some users. E-Health has high confidentiality experience among cancer patients[39] and has the potential to be cost-effective and to improve patient empowerment[40], psychological well-being,[39,41] and health-related quality of life.[41] Future studies should aim at in-depth knowledge about the use of the community in terms of not becoming a member of the community, reasons for stop using, reasons men visit the community less often and whether additional elements should be added in particular to make it more attractive for men. It is also worth exploring whether psychological interventions like cognitive-behavioral therapy could be safe and effectively delivered online to AYA cancer patients.[42] We expect that the AYA community will expand in terms of members and reputation in the future, since it only recently expanded from the regional to the national level.

In conclusion, the Dutch online AYA community facilitates peer support in a secure digital environment and, in particular, leads to expressing feelings, exchanging information and better coping with cancer. Health care professionals should play an active role in drawing attention to the existence and the possible benefits of the online AYA community.

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Chapter 8

Experiences of parents and general practitioners with end of life care in adolescents and young adults (AYAs) with cancer

Suzanne EJ Kaal, Noortje MJ Kuijken, Constant AHHVM Verhagen, Rosemarie Jansen, Petra Servaes, Winette TA van der Graaf

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Abstract

This study aims to analyse the experiences of Dutch bereaved parents and general practitioners (GPs) with palliative care of AYAs (18-35 years) in the terminal stage. Fifteen parents and nine GPs involved with nine deceased AYAs filled out questionnaires and were interviewed by telephone, respectively. In general, the parents were satisfied with the emotional care they themselves received and the medical care that their child received. The GPs were very satisfied with the cooperation with the palliative team. Gaps are present in the areas of symptom control, communication between hospital professionals and parents, aftercare and transition between hospital and GP.

Introduction

Adolescents and young adults (AYAs) aged 18 to 35 years and diagnosed with cancer, have a 5-year survival rate of 77% and approximately one quarter of them dies of cancer.[1,2] Compared to palliative care for children, the care of AYAs has an extra dimension. Namely, it should take into account the normal physical and psychological changes associated with this life phase, including attainment of independence and social skills, peer acceptance, and self-image building.[3]

The terminal stage of AYAs is not only characterized by specific problems for patients, but also for parents. Parents are conflicted with trying to balance between taking care of their child on the one hand, and respecting his/her autonomy on the other hand. Parents may feel helpless and sometimes even feel excluded by the health care system.[4,5] Furthermore, physical pain and lack of medical and emotional care at the moment of death of their child are important issues that should be addressed to reduce long-term distress in bereaved parents.[6] Sharing the emotional burden with others, professionally and socially, and good aftercare appear to benefit this process of bereavement.[7,8] However, many parents report the contact with health care professionals after their child's death to be insufficient.[4] Previous research has also shown that informal caregivers (i.e. family or friends) would like to receive more information about the patient's prognosis and process of dying, and more support in increasing their knowledge and skills concerning pain and symptom control.[9-13]

In general, little is known about the experiences of parents who have lost a child at AYA age. Furthermore, general practitioners (GPs) are rarely confronted with a terminally ill AYA. In 2013 only 227 patients aged 15 to 34 years died of cancer in the Netherlands.[14] Information on the GPs' experiences with providing palliative care to this group of patients and their families is also lacking. In order to gain insight into the experiences and needs of bereaved parents and GPs concerned with palliative care of AYAs in the terminal stage this study aims to answer the following research questions: 1) How do bereaved parents experience the palliative care for their child and (after)care for themselves? 2) What are parents' experiences with social support around the loss of their child? 3) What is the impact of the loss of a child on parents' psychological wellbeing? and 4) How do GPs experience the palliative care of a terminally ill AYA and his/her family?

Methods

Participants

Fifteen parents (eight mothers, seven fathers) of nine deceased AYAs participated in this study. The AYAs, aged 18 to 35 years, had died of cancer in the past two years and had been treated by the Department of Medical Oncology of the Radboud University Medical Center. During the last three months of their lives, the AYAs had lived with their parents and had been cared for by them. A total of nine GPs involved with the care for eight AYAs also participated in the study (one AYA had two GPs). Ethical approval for the study was obtained from the local certified Medical Ethics Committee.

Procedure

The parents of ten AYAs were approached by their child's former Medical Oncologist to participate in this study. Fifteen parents of nine different AYAs agreed to participate and filled out four questionnaires. Nine of the ten approached GPs agreed to participate and were interviewed by telephone (tape-recorded). The interview questions for the GPs were formulated by NK and SK (table 1).

At home, the parents filled out the following questionnaires:
To measure parents experience with palliative care for their child and (after) care for themselves, a general, non-validated questionnaire was used. It was derived from a previous questionnaire developed by the research team, measuring experiences in partners from deceased patients. It consisted of 51 items on: demographic characteristics (marital status, level of education); the period during which the child was terminally ill and the period thereafter; the relationship with the child and their partner; emotional, practical and professional support; and communication with GP and hospital.

To measure parents' experiences with social support around the loss of their child, the Dutch *Inventory for Social Reliance (ISR)* was used. It assesses qualitative aspects of social support and contains 11 items on a 4-point scale. Three factors are distinguished: *potentially present (but not necessarily given) emotional confidentiality* (the perceived possibility to share joy and sorrow with each other, five items, range 5-20), *actual confidentiality* (actual sharing joy and sorrow with other people, three items, range 3-12) and *mutual visiting* (visiting family and friends reciprocally, two items, range 2-8).[15,16]. Parents completed the ISR twice; once to measure current social support (ISR-now) and once to measure the social support received during the child's illness (ISR-then).

Table 1: Questions asked to GPs' in the telephonic interviews about the period delivering end of life AYA care

1. How did you perceive the cooperation between intramural physician/team and yourself?
2. Did you perceive enough support (emotional, practical) from the hospital team?
3. How would you describe the relationship with the AYA and the parents in the terminal phase?
4. Did you feel capable enough to deliver AYA end of life care?
5. Would extra training be helpful in delivering better AYA end of life care?
6. Have you experienced any differences in comparison to delivering adult palliative care?
7. Do you have the impression that the parents currently have problems concerning the loss of their child (depression, anxiety, complicated mourning)?
8. Have you been involved in aftercare for the parents after their child passed away?
9. Do you have any suggestions/recommendations to improve end of life AYA care regarding cooperation, communication?

GP: General Practitioner

Table 2: Symptoms During the Last Three Months Before Death According to the Parents

Symptom	Parents of AYA															Total	%
	1	1	2	2	3	3	4	5	5	6	7	7	8	9	9		
Pain	x	x	x	x	x	x	x	x*	x*	x	x	x	x	x	x	15	100
Fatigue	x	x	x	x	x	x	x	x	x	x	x		x	x	x	14	93.3
Nausea	x	x	x*		x	x		x*	x	x	x	x	x*	x	x	13	86.7
Anxiety	x	x			x		x*	x	x	x*			x	x	x	10	66.7
Somnolence	x	x					x	x	x		x	x			x	8	53.3
Constipation	x*	x*					x	x	x					x	x	7	46.7
Insomnia			x	x			x						x			4	26.7
Anorexia				x			x			x						3	20.0
Dyspnoea							x									1	6.7
Depression															x	1	6.7

In assessing psychological wellbeing of the parents, two questionnaires were used. The validated Dutch translation of the *Inventory of Traumatic Grief (ITG)* measures the intensity of mourning and differentiates between normal and 'potentially problematic' mourning.[17] It consists of 29 items rating on a 5-point scale, with a range from 0 to 116. A score above 39 indicates complicated mourning, and a score above 87 indicates severe complicated mourning for which specialized treatment should be strongly advised. The validated Dutch translation of the *Hospital Anxiety and Depression Scale (HADS)* measures anxiety (7 items) and depression (7 items) during the past week. Per item a score between

0 and 3 is assigned, leading to a score range of 0-21 for anxiety and depression trait, respectively. A total score of 12 or above or a score of 8 or above on one of the subscales indicates the need for involvement of a specialized caregiver.[18,19]

Analysis

For the analysis of the results of the questionnaires, descriptive statistics were calculated. The interviews with the GPs were analyzed qualitatively and answers were clustered in different themes.

Results

Results of the general questionnaire

Demographics of the parents

Fifteen parents (of which six couples, eight mothers, seven fathers) of nine AYAs filled out the questionnaires. The parents of one AYA were divorced. At the time of participation, the median age of the mothers was 51.5 years (range 48-59 years) and of the fathers 55.0 years (range 51-66 years). The majority of the participants (60%, three fathers, six mothers) had an intermediate educational level. The time between the death of the AYA and participation in the study ranged from 3 months to 2 years. At the moment of death, the AYAs had a median age of 21.0 years (range 18-28 years).

Summary of parents' experiences

Table 2 represents parental report of the symptoms that the AYAs had suffered from during the last three months before death. The most frequently mentioned symptoms were pain, fatigue, nausea, anxiety, somnolence and constipation. Of these, constipation, nausea, anxiety and pain were not adequately palliated. Five parents (33%) experienced problems in communication with hospital-based healthcare workers and two parents reported communication problems regarding the role and accessibility of the GP. The majority of the parents indicated that their relationship with their child before he or she got ill was very good. Five parents stated that they felt emotionally more connected with their child. The majority of the parents experienced sleeping problems (80%). Six parents (40%) had mental complaints (depression or anxiety) after their child had passed away. Eight of the fifteen parents (53%) reported using professional bereavement counseling after their child's death, with which the majority was satisfied. Almost three-quarters of parents reported their expectations of the GP and the hospital in terms of guidance, medical care, responsibility and accessibility were fulfilled. One parent reported a perceived lack of empathy on behalf of the GP, two felt insufficiently supported and one reported a lack of acknowledgement concerning mistakes made by the GP. One parent missed having contact with the hospital after her child's death.

Results of the ISR, ITG and HADS

Table 3 shows the results of the ISR-now and ISR-then. The mean scores on the three factors were comparable at both moments for mothers as well as fathers. Strikingly, the mean scores on *potential confidentiality* were higher during their child's illness than at the time of participation in this study. The mean scores on *actual confidentiality* and *mutual visiting* of the fathers were also higher during their child's illness than at the time of participation. The results of the ITG show that five mothers (63%) and four fathers (57%), (60% of all participants) scored above 39, which is indicative for complicated mourning. The results of the HADS (Table 4) show that four parents (27%) scored 8 or above on the anxiety scale and nine parents (60%) scored high on the depression scale. Ten of the fifteen (67%) parents scored above cut off point on the total HADS scale.

Results of the interviews with GPs

In general, the GPs were positive about the collaboration with the intramural physician. One GP reported that his role had been ancillary because of the very close bond between patient and oncologist. Three of the nine GPs were dissatisfied about the collaboration with the intramural physician. This was due to problems in communication, which was based mainly on letters. Regular telephonic feedback, according to the GPs, would create an open atmosphere in which mutual support and teamwork could prevail. Four GPs reported that the collaboration with the palliative team was found to be very instrumental (well accessible, good advice and support). Seven of the nine GPs experienced the palliative care for an AYA as more difficult because of the age of the patient. They reported an emotional feeling of "unfairness" and a greater empathy for the family. Another complicating factor of this care was the uncommunicative character of the AYA (reporting symptoms very late, not willing to talk about dying).

Table 3: Results of the Inventory for Social Reliance-Now and Inventory for Social Reliance-Then

Couple	Female (n = 8)						Male (n = 7)					
	Potential confidentiality		Actual confidentiality		Mutual visiting		Potential confidentiality		Actual confidentiality		Mutual visiting	
	Now	Then	Now	Then	Now	Then	Now	Then	Now	Then	Now	Then
A	17	20	11	10	7	7	13	13	6	7	5	6
B	14	16	7	7	6	5	14	16	9	7	6	7
C	13	12	7	7	6	6	12	13	6	6	5	4
D	13	19	6	7	6	7	11	14	4	6	6	7
E	17	20	7	7	6	5	20	20	6	7	3	4
F	8	7	6	6	4	5	5	11	4	5	5	5
No couple							19	19	6	7	5	4
No couple	9	12	7	8	3	5						
No couple	16	18	8	7	7	5						
Mean	13.38	15.50	7.38	7.37	5.63	5.63	13.43	15.14	5.86	6.43	5.00	5.29
(SD)	(3.42)	(4.72)	(1.60)	(1.19)	(1.41)	(0.92)	(5.06)	(3.34)	(1.68)	(0.79)	(1.00)	(1.38)

* Symptom not adequately palliated according to parent AYA, adolescent and young adult

Table 4: Results of the Hospital Anxiety and Depression Scale

Couple	Female		Male	
	Anxiety	Depression	Anxiety	Depression
A	4	5	1	3
B	4	6	4	3
C	7	8	5	9
D	5	2	13	11
E	15	14	5	7
F	0	15	7	19
No couple			8	13
No couple	10	13		
No couple	7	12		
Mean (SD)	6.50 (4.50)	9.37 (4.78)	6.14 (3.76)	9.29 (5.71)

Discussion

This study consists of an analysis of the experiences of parents and GPs with end of life care aspects of deceased AYA cancer patients. The majority of the parents were satisfied with the emotional support they received and the medical care their child received by the hospital and GP during the terminal stage. However, we found that more than half of the parents noticed their child was suffering and these symptoms were not always well controlled.

In accordance with previous studies, it was found that some improvements are needed in the communication between hospital team and GP.[8,12,13,20,21] The transition period from hospital to GP-guided care proved to be a risky period with regard to exchange of contextual and disease related issues. Also, parents reported communication problems with hospital-based healthcare workers and regarding the role and accessibility of the GP . The input of the palliative team was highly appreciated by GPs, underlining the fact that integrated care, with close collaboration between hospital and other health care workers directly involved AYA care, is optimal.[13,22]

Psychological distress in bereaved parents is illustrated by the fact that 60% of them had scores indicative of complicated mourning which is slightly higher compared to parents who experienced grief related separation distress after losing a child (median age of death 8.3 years) [23]. However, we found substantially higher scores on depression and anxiety compared to parents who lost a child at a younger age. [23,24] Almost half of the parents did not receive any aftercare and reported missing this kind of support. It has been confirmed in literature, suggesting that offering aftercare is an important part of standard professional support.[11]

Strengths of this study include that the results are based on the perspective of both the care receivers as well as the care providers. Moreover, it is the first analysis of this kind in the Dutch health care setting. Limitations are the retrospective study nature with a different length of time between the death of the AYA and the participation in this study (recall bias, normal grief regresses over time), as well as the small number of participants. Disease severity and length of time under palliative care have also not been addressed. Nevertheless, the results of our study are valuable and can form the basis for further research on and improvement of end of life AYA care.

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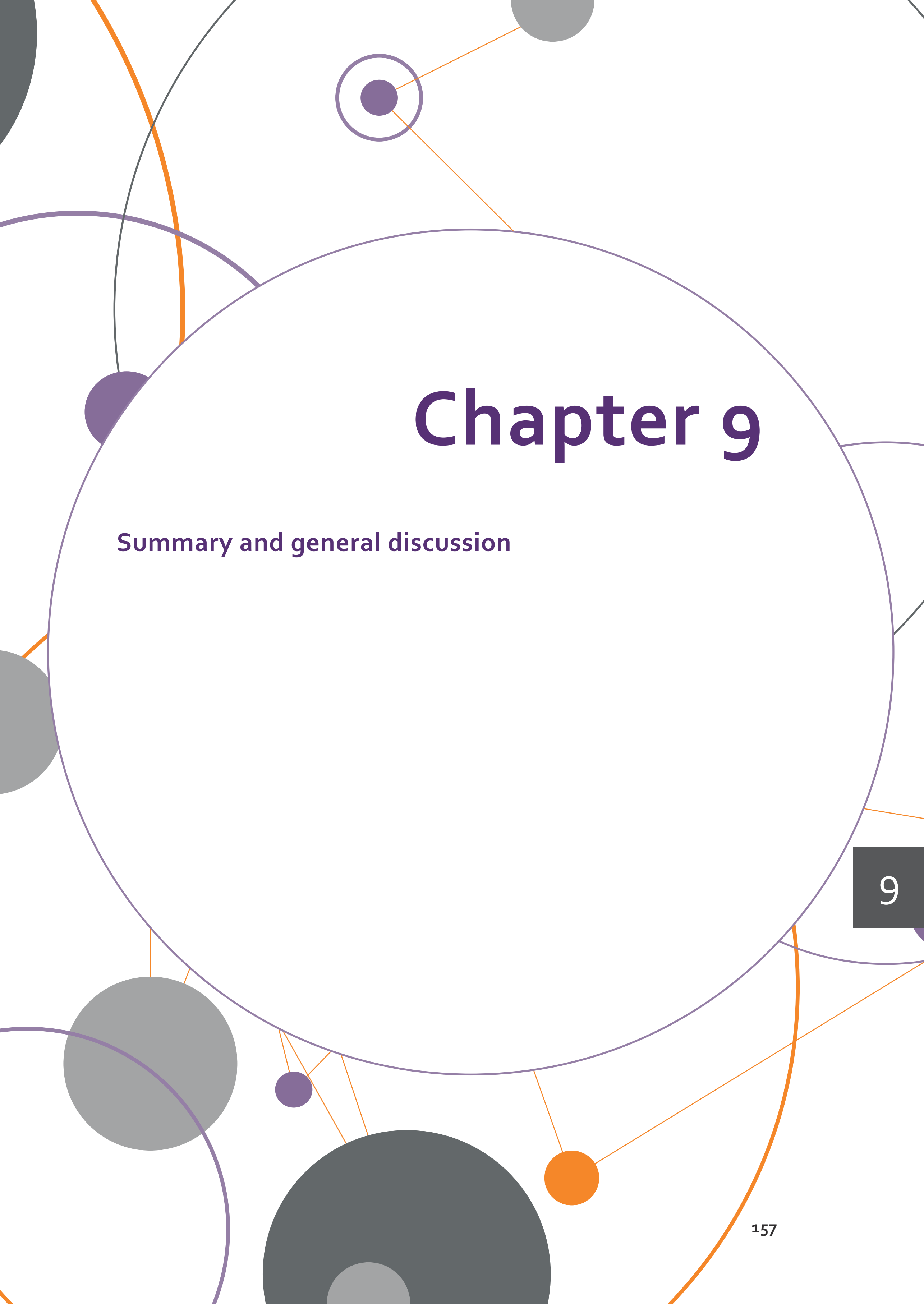

Chapter 9

Summary and general discussion

This thesis focused on aspects of health-related quality of life (HRQoL), psychosocial outcomes and adaptations and supportive and palliative care issues among adolescent and young adult (AYA) cancer patients. In this final chapter, the previous chapters are summarized and discussed. Practical implications along with recommendations for future research are formulated.

Part I: Health-related quality of life, psychosocial outcomes and adaptations

HRQoL is one of the most widely used patient reported outcomes (PRO). Measuring HRQoL provides insight in the effect of cancer and its treatment on physical, psychological and social functioning. **Chapter 2** describes the top ten HRQoL priorities relevant to AYA cancer patients (stratified by gender, cancer type, treatment intention, partner status and having children) and whether there is a discrepancy between items prioritized by AYA cancer patients and oncology health care professionals (HCP). Patients (n=83) scored significantly lower on negatively formulated HRQoL issues (e.g. fatigue, coping difficulties, feeling isolated) and significantly higher on positive formulated issues (e.g. support from others, overall physical health, happiness) compared to HCP (n=34). The most important issues for AYA cancer patients were: perceived support from others, distress about initial cancer diagnosis, distress for family, overall quality of life and happiness. HCP perceived distress about initial cancer diagnosis, distress for family, cancer treatment distress, interference of illness with employment/study and fatigue as most important for AYA. The top ten priorities of patients versus perceptions of HCP overlapped for five out of ten items. It was concluded that AYA cancer patients perceived most negative HRQoL items as less problematic compared to HCP. The discrepancy between patients and HCP illustrates the importance of patient participation, i.e. involving patients in organizing and prioritizing their own (psychosocial) care, and broadening the problem-focused perspective of HCP to positive outcomes in delivering supportive care.

In **Chapter 3** we report on prevalence and correlates of fear of cancer recurrence (FCR) which is a frequently reported problem among cancer patients in general. Previous research has shown that younger age is associated with higher levels of FCR. However, little attention has been given to date about how FCR manifests itself among AYA cancer patients. High FCR was experienced in 62% of the AYA cancer patients, which was higher than reported in previous studies among mixed adult cancer patient samples. High FCR was significantly associated with lower levels of social and psychological functioning and overall HRQoL and higher levels of psychological distress. These results illustrate that FCR is a significant problem among AYA cancer patients. HCP should pay specific attention to this problem, for instance with a screening instrument for FCR, and the provision of appropriate psychosocial care when needed.

Chapter 4 focused on the prevalence, impact, and correlates of severe fatigue in AYA cancer patients. Severe fatigue, based on a validated cut-off score, occurred in 48% of participating AYA cancer patients visiting the AYA outpatient clinic. This proportion is significantly higher compared to the proportion of severely fatigued gender and age matched population-based controls, in which only 20% scored above the cut -off. We demonstrated that severely fatigued AYA cancer patients reported significantly lower HRQoL in the physical, psychological, social and spiritual domain. Fatigue severity was associated with female sex, being unemployed (or not studying), late stage cancer at diagnosis, receiving active treatment at the time of study participation, palliative intent of treatment, and having had radiotherapy as part of cancer treatment. In addition, FCR and higher psychological distress were associated with higher cancer-related fatigue scores. The findings of this study emphasize the importance of careful attention for fatigue in this population. Screening for the presence of severe fatigue at regular intervals as well as the identification of treatable contributing factors (e.g. anaemia, hypothyroidism, psychological distress, and sleep disorders) is warranted not only during cancer treatment but also after completion of treatment.

Chapter 5 entails an overview of the literature on post-traumatic growth (PTG) and resilience among AYA cancer patients. Qualitative interview studies showed that AYA cancer patients report PTG and resilience: PTG is described by AYA cancer patients in terms of benefit finding, including changing views of life and feeling stronger and more confident, whereas resilience is described as a balance of several factors, including stress and coping, goals, optimism, finding meaning, connection and belonging. Quantitative studies showed that sociodemographic and clinical characteristics were not associated with PTG. Enduring stress was negatively, and social support positively associated with PTG. Symptom distress and defensive coping were negatively and adaptive cognitive coping was positively associated with resilience. Both PTG and resilience were positively associated with satisfaction with life and HRQoL. Resilience was found to be a mediator in the relationship between symptom distress and HRQoL. Two interventions aiming to promote resilience, a stress management and a therapeutic music video-intervention, were not successful in significantly increasing overall resilience. Most AYA cancer patients reported at least some PTG or resilience. Correlates of PTG and resilience, including symptom distress, stress, coping, social support, and physical activity, provide further insight to improve the effectiveness of interventions aimed at promoting these positive outcomes and potentially buffer negative outcomes.

One of the hypothesized mechanisms behind resilience and PTG is empowerment. The difficulties AYAs encounter during a cancer experience may result in a reduction or absence of empowerment. The aims of **Chapter 6** were to assess levels of empowerment and associated (demographic, clinical, or psychological) factors and examine the association between empowerment and HRQoL among AYA cancer patients. Multivariate analysis demonstrated that autonomy (self-awareness, capacity for managing new situations) and social support were positively associated with empowerment. Coping difficulties were found to be negatively associated with empowerment. Empowerment was independently associated with physical, psychological, social, religious and overall HRQoL. Recognizing these patients as candidates for empowerment interventions could help to improve HRQoL in AYAs.

Part II: Supportive and palliative care

It is of utmost importance to provide the best supportive care to each AYA cancer patient and its caregivers. In **Chapter 7** the user statistics, evaluation and content analysis of a Dutch secure online support community for AYA cancer patients was described. Since the start in 2010 the community has grown to 433 members (71% female; mean age at diagnosis 25.7 years) from 52 out 91 hospitals in the Netherlands in 2017. A national questionnaire survey among 66 AYA cancer patients showed that 30 of them used the community on a regular basis. They indicated that the use of the community resulted in acknowledgement and advice regarding problems (56%) and the feeling of being supported (63%). Almost half of the respondents felt less lonely and 78% experienced recognition in other AYAs cancer stories. Anonymized content analysis showed that the majority of the online discussions encompassed emotional and cognitive expressions, and emotional support. It was concluded that AYA cancer patients often lack the option to meet each other in person. The secure Dutch online AYA community can help AYA cancer patients to express feelings, exchange information, address peer support and is found helpful in coping with cancer. Its use would benefit from promotion by health care professionals. Of note, only few AYA patients (n=14) gave informed consent for content analysis, in spite of their knowledge that their data would be analysed in an anonymous form.

In **Chapter 8** the experiences of Dutch bereaved parents and general practitioners (GPs) with palliative care of AYAs in the terminal stage were analyzed. Fifteen parents and nine GPs involved with nine deceased AYAs filled out questionnaires and were interviewed by telephone, respectively. In general, the parents were satisfied with the emotional care they themselves received and the medical care that their child received. The GPs were very satisfied with the cooperation with the palliative team. Gaps were identified in the areas of symptom control, communication between hospital professionals and parents, aftercare, and transition between hospital and GP.

General discussion

Part I: Health-related quality of life, psychosocial outcomes and adaptations

Adolescent and young adult (AYA) cancer patients: an understudied population with regard to psychosocial outcomes and its correlates

Historically, children with cancer have gained a lot of attention, partly because successes in treatment have led to an increasing number of survivors reaching adulthood, in which long-term and late effects of treatment, so-called survivorship issues, affect HRQoL, even decades after end of treatment[1-3]. Surprisingly, AYA cancer survivors have not had this attention while they outnumber paediatric cancer cases, still have cancer at a very young and unusual age, and -as total group- have a 80% chance to survive, with also the risk of survivorship issues[4]. The good news is that over the last two decades the attention for AYAs with cancer has grown substantially, e.g. reflected by the development of AYA oncology guidelines[5] and the annually recurring global AYA oncology conference. Stuck between paediatric and adult oncology patients, this age group has specific issues and accompanying unmet informational and supportive care needs[6]. AYA age-specific care can only be delivered after examination of the HRQoL problems AYA report and after a method or procedure has been developed to assess which AYA patients will face more issues and may develop impaired physical, psychological or social functioning. Given the lack of systematic identification of AYA patient subgroups that might be more susceptible to poor health outcomes (e.g. impaired HRQoL, more symptoms, low empowerment) there is a high demand for relevant and structured research. The role of sociodemographic and treatment-associated risks and/or psychosocial factors (social support, coping, autonomy) for impaired health outcomes, remains largely unknown. With the aim of developing an optimal AYA supportive care program with age-adjusted guidelines we thus require insight not only who is more at risk, but also when and why they are at risk. Therefore, the first part of this thesis addressed the HRQoL issues of importance to AYA with cancer and its correlates.

Negative outcomes

It was shown that AYA cancer patients rated negative HRQoL issues (e.g. financial issues, concentration/memory problems) as less important compared to health care professionals (HCP). However, some specific problems like cancer-related fatigue and fear of cancer recurrence (FCR) were highly prevalent among AYAs, which indicates that screening on these symptoms might be warranted as they highly affect HRQoL. Successful interventions that target FCR are developed for adult cancer patients including mind-body interventions (utilizing the mind's capacity to affect the body and its physiological responses e.g. mindfulness), interventions aimed at more effective patient-provider communication, and handling stress through counseling[7,8]. Future research should examine if these interventions are feasible and effective for AYAs.

Severe cancer-related fatigue was found to be more prevalent in AYAs than in healthy peers. A recent study showed similar results but also reported that AYA cancer patients had higher levels of fatigue than older cancer patients[9]. Interventions aimed at diminishing fatigue among adult cancer patients in general have been examined previously. Exercise (i.e. aerobic, anaerobic or both), psychological (i.e. cognitive behavioural or psycho-educational therapies), and exercise plus psychological interventions improved cancer-related fatigue during and after primary cancer treatment, whereas pharmacological interventions did not[10]. Whether AYA suffering from severe fatigue equally benefit from these interventions is subject for further research. It may well be that the requests posed by society on people of this young age make AYA cancer patients more vulnerable for (cancer-related) fatigue.

Although AYA cancer patients rated several HRQoL issues as less important compared to HCP, the overall HRQoL of the AYA cancer population described in the literature is worse compared with normative populations[11,12]. Some interventions that aim to promote HRQoL of AYA are described in the literature[13-15]. A recent systematic literature review on health promotion and psychological interventions concluded that interventions delivered face-to-face and those that facilitate peer-to-peer support are promising. Harnessing social media and technology to deliver interventions is likely to increase and these modes of delivery require further investigations[13]. Very recently a Smartphone application, consisting of a symptom and activity diary, a communication network and forum and an information bank, has been developed aiming to improve HRQoL in AYA cancer patients[14]. A prospective, non-randomized study showed that offering a fitbit (a digital activity tracker that measures physical activity) or other wearable technology at time of cancer diagnosis improves HRQoL in AYAs over time, probably through mechanisms as reducing fatigue, enhancing physical activity and prevention of social isolation[15].

Positive outcomes

This thesis showed that post-traumatic growth (PTG) and resilience are relevant positive psychosocial health outcomes in AYA cancer patients. AYA rated negative HRQoL issues less high compared to HCP, showing that most AYA perceive themselves as resilient and are able to overcome the negative consequences of having cancer. Notably, this may also illustrate the fact that young people not have a reference frame and do not always oversee already the consequences of cancer and its treatments they may experience later in life, which is in contrast to the perception of (experienced) health care professionals. A longitudinal cohort study among AYA identified more benefits than burdens throughout cancer treatment. The most prevalent benefit was a positive changed sense-of-self. Over time participants tended to focus more on personal strengths and life purpose[16]. Much of today's psychosocial oncology research is derived from Selye's theoretical stress and coping models, in which an emotional response to traumatic events or conditions may be experienced as "distress" (negative) or "eustress" (positive)[17]. When applying the stress coping theory to investigations of patients' psychosocial adaptation to cancer, it suggests that it is theoretically possible to experience both positive and negative responses to cancer simultaneously. In previous literature positive adaptation to traumatic life events, including serious illness, as PTG has been conceptualized [18,19]. Positive changes reported by cancer survivors have included a greater sense of closeness to others, higher appreciation of everyday life, recognition of new possibilities in life, a sense of personal strength, and deeper spirituality[20]. In a semi-structured interview study of AYAs with cancer[21], two recurrent topics emerged: (1) loss of control resulting in a sense of frustration and anger; and (2) benefit finding such as improved personal attributes and strengthened relationships. Recently it was shown that PTG has a direct positive predictive effect on mental HRQoL but not on physical HRQoL among AYA with cancer[22]. One potential implication of the findings of this thesis is that helping AYAs with cancer who experience low or decreasing levels of PTG to find meaning and benefits in the cancer experience, may help improve their mental adjustment. This may be accomplished by encouraging the reappraisal of the situation (positive reframing) or the emotional disclosure of inner feelings and fears[23]. A written emotional disclosure intervention, whereby adult breast cancer survivors were randomized to write about positive thoughts and feelings related to their cancer, showed that those who wrote down positive feelings reported less physician visits for medical comorbidities and distress than survivors who wrote down facts of their experience [23]. In addition, two cognitive-behavioural interventions for adult cancer patients, that included elements of coping skills training, relaxation exercises, conflict resolution and emotional expression, had beneficial effects on PTG [24,25]. Another way to enhance PTG, may be regular physical activity. The physiological benefit of physical activity may be stress reduction. Physical activity may also increase levels of social support for AYA cancer patients and serve as an active coping strategy to decrease levels of distress[26]. In addition, physical activity can improve AYA cancer patients' self-efficacy levels, whereby the experience of positive feelings may be enhanced. As PTG predicts mental well-being, interventions focused on improving PTG are likely beneficial in the early post-treatment period.

This thesis also showed that empowerment was independently associated with physical, psychological, social, religious and total HRQoL. Identification of correlates of empowerment (e.g. autonomy, social support, female sex and coping difficulties) will help us to develop interventions to reinforce empowerment. For example, interventions with cognitive behavioural therapy elements through eHealth have proven to be effective (e.g. BREATH study)[27]. A recent study showed that the majority of lymphoma patients reported that they would like to receive feedback on their questionnaires answers, comparison of their own complaints with those of other patients or their own score over time[28]. In response to this need, the LIVE trial has been developed to examine whether feedback to patients on their patiënt reported outcomes (PROs) and access to a web-based, self-management intervention will increase self-management skills and satisfaction with information, and reduce psychological distress in lymphoma patients[29]. Such a PRO and self-management intervention focusing on age-specific aspects could also be an option for AYA to increase their self-management skills and increasing empowerment.

Part II: Supportive and palliative care

The organisation of oncology health care in the Netherlands, with a clear separation between paediatric and adult oncology, was not ideally suitable for AYA cancer patients with their age-specific HRQoL issues. Traditionally, when reaching adulthood, patients of 18 years or older are treated in adult treatment centres. These centres often deliver care through disease-focused models in which high patient volumes and limited infrastructure challenge the ability to address the specific care needs of AYAs with cancer. In addition, AYA patients represent a small percentage of adult patients with cancer and thus health care teams have less experience and expertise with this population.

AYA oncology in the Netherlands

During the realisation of this thesis, there has been considerable development of AYA cancer care worldwide and also in the Netherlands. In 2009, the Department of Medical Oncology in collaboration with the Department of Medical Psychology of the Radboud university medical center (Radboudumc) launched the AYA Expertise Platform, a close collaboration of AYA cancer patients and health care professionals. The main goal of the Platform is to improve the care for and the quality of life of AYA cancer patients by developing structural, standardized, comprehensive and patient-centered guidelines for AYA cancer care. An AYA outpatient clinic was launched where AYA cancer patients, regardless of their treatment status, type and intent of treatment, could address their age-specific questions to a dedicated multidisciplinary AYA team (expert nurse, medical oncologist, psychologist, social worker and a clinical physician occupational health in oncology). The AYA outpatient clinic turned out to be an easy accessible service for AYA cancer patients. In 2010, an online community named AYA4 (All Information You've Asked for) was developed by and for AYA cancer patients treated at the Radboudumc. The AYA4 online community became available for all AYA cancer patients in the Netherlands in 2014. One of the aims of this thesis was to examine how these new initiatives were rated by AYA cancer patients.

Online initiatives: the road ahead

Since AYA are digital natives and have grown up with internet, social media and other digital technologies, it seems reasonable to develop online supportive care interventions. By doing so, it is of the utmost importance to develop these interventions in co-creation and co-participation with AYA cancer patients. Before the development of the AYA online community, AYA cancer patients were interviewed about their needs and problems during and after the cancer journey. Based on their input, the AYA online community was developed. This thesis showed that the online community can help AYA cancer patients to express feelings, exchange information, address peer support and is found helpful in coping with cancer. Whether the AYA online community has to be expanded over the next years, for whom and in which form is subject of further research. In the forthcoming years we should focus on which patients have most advantage of using the AYA online community and whether elements should be added to make it more attractive. For example, it might be interesting to explore if psychological interventions like cognitive-behavioral therapy or self-management interventions could be delivered safely and effectively online to AYA cancer patients in need of such intervention. In addition, it is worth exploring if the community can be used for direct face-to-face digital interaction between

AYA patients and health care professionals for example to educate about and discuss age-specific topics (figure 1). At the start of the community in 2010 other social media like what's app were not available and nowadays are being used by 70% of the worldwide population. Moreover, it is interesting to examine if the positive effect of the AYA online community differs between so-called 'lurkers' (members of an online application who read content, but not actively post content or discuss with other members, in general the vast majority) and active members (in general a small minority). In its current form the AYA online community is not attractive for users with handheld electronic devices. The process of co-creation and co-participation has developed strongly over the last years. Recently a co-creative smartphone app for AYA with cancer was developed in Denmark. Based on the input of patients the app has now three primary features: a symptom and activity diary; a supportive communication network between app users; and a "one-stop-shop" information bank with practical information as well as links to patient organizations and other resources[14]. It might be interesting to integrate this type of app to the online community in order to offer this information more easily to users with handheld electronic devices (smartphone). In The Netherlands we recently created the MATCH app which aims to (re-)connect AYA with their peers and stimulate communication and compassion[30]. This app was an answer to the desire of AYA, their family and friends who indicated a need to stay in contact after a cancer diagnosis. The usefulness of the MATCH app is currently being studied.

One of the major challenges in this modern digital era with rapid evolvement of online interventions is to examine whether these interventions are truly helpful for users. The classical randomized controlled trial is a solid but time-consuming method to determine the usefulness of a new digital application. When results are awaited, sometimes over several years, patients do not have access to this potentially helpful intervention and seek help for their problems for example by consulting a physician, psychologist or social worker. Meanwhile, new applications are being developed even before the previous ones had proven to be effective (or not). There is a tendency to develop, test the effectiveness and implement new applications during the use by the target population[31]. If we want to study whether an online intervention is effective, we first have to adjust our expectations about the feasibility of such research project. Then, we have to predefine clinically relevant end points which are realistic and robust. For example, when testing an online application in AYA, we can focus on end points such as less health care consumption for psychosocial problems or faster return to work. We have to look for quicker evaluation methods which can give an acceptable degree of evidence. Also, from the very start of any intervention we should monitor engagement and early markers of possible effectiveness or for signs that the intervention is not working. Lastly, whether this continuous process of renewal and improvement of digital interventions is cost-effective will be a subject of debate and an important topic for future research.

Figure 1: Age-specific topics in the AYA cancer patient population

Palliative and end-of-life care

As one in five AYA patients dies of cancer, it is important to deliver palliative and end-of-life care adjusted to the needs of this age group. This thesis showed that general practitioners (GP) involved in AYA end-of-life care were very satisfied with the cooperation with the palliative team, but improvements have to be made concerning symptom control, communication between hospital professionals and parents, aftercare, and transition of care between hospital and GP. Previous research showed that AYAs reported anticipatory grief over their lives that have not yet been lived and that they may be reluctant to face the irreversibility and progression of their disease. This may lead to delays in the start of palliative and end-of-life care[32]. It was also shown that AYAs who die in the hospital tend to use palliative care services very late in the course of their cancer and often undergo aggressive treatment until death is near[33]. Therefore, it should be encouraged to introduce palliative care in an early stage into standard supportive clinical care for AYA, meaning from the time of diagnosis until the time of death or cure. The palliative care should be provided by a multidisciplinary team with expertise in understanding the psychosocial, emotional, developmental, and financial issues that are unique for AYAs[5]. With regard to end-of-life care, a recent study showed that end-of-life care preferences for AYA may differ from those of the adult population[34]. AYA patients more frequently died at home compared to older adults and received more frequently chemotherapy in the last month of their life. Discussions about end-of-life preferences should begin at the time of starting (palliative) treatment, but details should be individualised according to the preferences of the AYA patient and family. Exploring individual preferences for end-of-life care and providing interventions that are specific to the needs of the AYA cancer patient population could significantly improve end-of-life care[35]. Physicians with expertise in end-of-life care should facilitate discussion of difficult issues such as nutrition/hydration, sedation, treatment cessation and place of death[36]. This thesis illustrates that timely involvement of the GP, good communication between hospital health care professionals and GPs regarding disease-related and contextual issues, are essential elements in delivering age-appropriate end-of-life care in AYA. Many AYA cancer patients indicate a preference for dying at home, yet most die in the hospital[37-39]. An advanced care planning document incorporating a discussion regarding goals of care, preferred location of care, preference for place of death, and consent to future intervention, including cardiopulmonary resuscitation could assist in pursuing this objective[34,35]. In the context of AYA end-of-life care it is worth mentioning that since 2009 there is a unique AYA hospice in the centre of The Netherlands (Leiden), a place where exclusively patients at AYA age with any form of incurable disease can spend the last phase of their life if dying at home is not preferred.

Limitations and future strategies

There are a few limitations of the studies in this thesis that are worth mentioning. First, the AYA patient study sample of chapter 2,3,4, and 6 was derived from a single center university hospital, the Radboudumc and therefore the study sample is limited. Since the Radboudumc is an expert center for bone sarcoma and testicular cancer, types of cancer that require intensive chemotherapeutic treatment, there might be an overestimation of disease severity of the entire AYA cancer population in which lower stage disease treated solely by surgery is more common. Future studies should undertake in a more mixed and larger population of AYA treated at hospitals (university and non-university) across the Netherlands. Second, although not uncommon in AYA research, the response rate among AYA patients was rather low (29%) as described in our chapters concerning HRQoL issues, fatigue, fear of cancer recurrence and empowerment. Previous psychosocial studies in AYA cancer patient populations also showed low response rates of 31%[40], 43%[41] en 52%[42], partially reflecting the difficulty in locating and recruiting a geographically mobile young adult population that in most cases are many years beyond therapy and no longer live with their parents. To improve the response rates, it would be beneficial to use in-person contact and, remarkably, patient-preferred paper-pencil rather than online surveys as suggested by Rosenberg *et al*, who examined the best method to recruit AYA patients (14-25 years)[43]. This might be different in AYA patient of older age. Other reasons for AYAs not participating in research could be that they are not interested in filling out questionnaires as they want to forget their cancer and just feeling 'normal' or that they are not aware of the importance of research or do not see themselves as an (AYA ex-) cancer patient, but just as a cancer patient. Future research in the AYA population will be more successful if we are better informed about the reasons for non-participation. To increase response rate, we could also ask their proxies to complete questionnaires. This adds valuable information for researchers and implicates that filling out questionnaires is 'just normal'. Third, we did not make use of AYA-specific HRQoL questionnaires, as they were not in place yet when we started with this research. In the meantime, a few AYA specific questionnaires have been developed. For example, adult and paediatric measures have been adapted to the specific issues relevant to AYAs and have AYA versions (PedsQL)[44] and there are measures which have been developed with and designed specifically for AYAs (CNQ-YP)[45]. In response to the need for AYA specific questionnaires the EORTC Quality of Life Group developed the EORTC-QLQ-AYA module with AYA specific issues (for example impact on family, dependency on others, interrupted education, workability) to measure HRQoL[46]. The first phase of the questionnaire development showed that AYAs with cancer have to deal with disrupted life plans and difficulty establishing romantic relationships which are likely to be more common to AYAs with cancer and might not be captured by existing HRQoL measures[46]. The Impact Of Cancer AYA (IOC-AYA) questionnaire has shown good psychometric properties to measure positive and negative HRQoL aspects in the AYA population[40] and could therefore also be an asset in future research using AYA-specific questionnaires.

Clinical implications and recommendations

Currently, AYA cancer care, research and education in the Netherlands is governed by the Dutch AYA 'Young and Cancer' Platform, which was founded in 2016. There are six regional comprehensive AYA networks, where an AYA expert university hospital with inpatient and outpatient facilities is connected with the surrounding regional hospitals. AYA care is delivered by means of an echelon system. Standard age-specific and psychosocial care for AYAs can be delivered nearby the patient coordinated from the nearest treating hospital. When an AYA needs more complex multidisciplinary care, this is covered by one of six regional expert centers across the country. The echelon system is currently implemented across the country. After enrolment it is essential to evaluate the AYA care program in terms of improvements in patient satisfaction, HRQoL, survival, and clinical outcomes (eg trial participation). Future studies need to provide objective evidence, with newly defined robust and predefined endpoints (for example less health care consumption for psychosocial problems or faster return to work), demonstrating the efficacy of critical components of the AYA care programs in order to create evidence-based guidelines, referral pathways, and education[32]. These predefined endpoints have to be established by a multidisciplinary team including AYA cancer patients, proxies, health care professionals, researchers and other stakeholders.

Although a recent paper showed that the distress thermometer is feasible and applicable in Asian AYA cancer patients to evaluate distress[47], one could argue if measuring distress is the best way. Based on the findings in chapter 5 and 6 we would make a plea to investigate whether it would be more suitable to measure empowerment by means of a '(em)power(ment) thermometer'. Focussing on measuring power or resilience, which has a more positive connotation, instead of problems or distress might be a more appealing and more informative way to assess positive HRQoL issues among AYA cancer patients.

Future research

The aims of future research should be to collect more data in a larger AYA patient population in the Netherlands. These data should focus on the most important HRQoL issues and correlates in a mixed AYA population with regard to age, sex, tumour type, disease stage, type of treatment and treatment intent (curative/palliative). The infrastructure of the Dutch AYA 'Young and Cancer' Platform enables us to perform research on a larger scale. In depth focus should be paid to developing (online) interventions to increase personal strength, reduce cancer-related fatigue and diminish fear of cancer recurrence. Future research should examine which AYA cancer patients will benefit most (or not) of the use of the AYA online community and to determine if the community has to be adapted or extended to the needs of the users. We should integrate existing online tools or applications aiming to support AYA into one larger online platform, where in the end AYA cancer patients can choose their type of online support or informational tool aiming to empower them. Also, we should focus on the user-generated content analysis available on the renewed AYA community available for AYAs, because this gives relevant patient-reported information. With regard to palliative and end-of-life care in AYA, the focus should be on a better transition from hospital-based care to home-based care and improvement of interprofessional communication. It is worth exploring if digital communication between patient, general practitioner and hospital health care provider, within the boundaries set by privacy regulations, can help in achieving these goals.

As chapter 2 illustrates the discrepancy between top 10 HRQoL issues between AYA and health care professionals, efforts should be undertaken to educate health care professionals on cancer at AYA age and to show them the pathways in delivering age-appropriate care across The Netherlands. It could be very helpful for health care professionals to visit the annual SPACE4AYA conference where state of the art information will be discussed on AYA care, education and research and interaction between AYA patients and health care professionals is stimulated[48]. Because cancer at AYA age is a rare disease, international cooperation in AYA research would increase the amount of data, accentuates intercultural differences and would facilitate the development of and enrolment in clinical trials for AYA. In addition, the AYA oncology agenda should be moved beyond high-income countries to support those in less-privileged circumstances[49].

Concluding remarks

AYA cancer patients have been recognised as a distinct population with unique medical and psychosocial needs. Health care professionals should be able to identify issues specific to the AYA population and recommend appropriate interventions with the aim of improving outcomes. AYA patients should have access to age-specific supportive care as well as medical subspecialty services accompanying their cancer diagnosis. Over the past years age-specific care for AYA in the Netherlands has made an impressive development, albeit with a continuously perceived pressure due to the lack of structured financial support. National governance of AYA care, research and education is covered by the Dutch AYA 'Young and Cancer' Platform. Now it is time to demonstrate the added value of this national program, which was once started based on vision and good will, but has evolved to a professional organisation, and we need to lobby for its financial sustainability. At the same time, we need to scale our research to a nationwide infrastructure for comprehensive health outcomes and intervention research. In this way we will be able to work towards more tailored care with the ultimate goal to generate better medical and psychosocial outcomes of AYA cancer patients.

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Nederlandse samenvatting

Kanker bij jongvolwassenen

Dit proefschrift gaat over AYA's, jongvolwassenen die in de leeftijd tussen 18 en 35 jaar kanker krijgen. De term AYA is afkomstig uit het Engels en staat voor Adolescent and Young Adult. Jaarlijks wordt in Nederland bij ongeveer 2700 nieuwe patiënten in de leeftijd van 18 tot 35 jaar de diagnose kanker gesteld. De soorten kanker bij AYA's kunnen in drie groepen verdeeld worden namelijk de staart van de kindertumoren ((zoals acute lymfatische leukemie of kinderhersentumoren), typische AYA-tumoren (zoals zaadbalkanker, Hodgkin lymfoom, melanoom, schildklierkanker) en het begin van de volwassen tumoren (zoals borstkanker, dikke darmkanker). Vanuit historisch perspectief is er veel aandacht uitgegaan naar kinderen (0-18 jaar) met kanker. Door betere behandelingen is de overleving van kinderen met kanker over de tijd verbeterd, maar de prijs van deze intensieve behandelingen is onder andere het ontstaan van late effecten. Opvallend genoeg is deze aandacht er niet geweest voor de AYA-leeftijdsgroep, terwijl de frequentie van nieuwe tumoren 5x zo hoog ligt als op kinderleeftijd, 80% van hen geneest en ook zij nog een lang leven voor zich hebben waardoor ook bij hen de impact van late effecten van kanker groot kan zijn. In de leeftijdsfase van adolescentie en jongvolwassenheid staat het behalen van ontwikkelingsmijlpalen centraal zoals het afronden van school of studie, een eigen identiteit vormen, relaties aangaan, een eerste baan krijgen, financieel onafhankelijk worden en een gezin stichten. Het krijgen van kanker op AYA-leeftijd kan ervoor zorgen dat de ontwikkeling stagneert en dat de AYA moeite heeft met functioneren op persoonlijk, sociaal en maatschappelijk vlak. AYA's kunnen vragen of problemen rapporteren zoals bijvoorbeeld op het gebied van relaties, vruchtbaarheid, studie, werk, verzekeringen of hypotheken. Deze zogenaamde leeftijdsspecifieke aspecten staan weergegeven in figuur 1.

Ontwikkeling van AYA-oncologie in Nederland

De laatste jaren is er aanzienlijke vooruitgang geboekt in de opzet van zorg voor AYA's wereldwijd alsook in Nederland. In 2009 werd het regionaal AYA Kenniscentrum Radboudumc opgericht door de afdelingen Medische Oncologie en Medische Psychologie van het Radboudumc in Nijmegen. Dit is een samenwerkingsverband tussen patiënten op AYA-leeftijd en zorgprofessionals betrokken bij de dagelijkse zorg voor AYA's met als doel de zorg voor en de kwaliteit van leven van AYA's te verbeteren. In 2009 werd de 1^{e} AYA-poli geopend in het Radboudumc. Dit is een laagdrempelig loket waar AYA's, ongeacht soort kanker en type behandeling, terecht kunnen met hun leeftijdsspecifieke vragen (zie figuur 1). De essentiële vraag van de zorgprofessionals bij elke AYA die de AYA-poli bezoekt is: wie ben jij en wat heb jij nodig? De patiënten die de AYA-poli bezoeken worden besproken in het multidisciplinaire team bestaande uit een verpleegkundig specialist, medisch psycholoog, maatschappelijk werker, klinisch arbeidsgeneeskundige oncologie en een internist-oncoloog, allen met specifieke kennis op het gebied van kanker op AYA-leeftijd. In 2010 werd de online AYA community opgericht met de naam AYA4 wat staat voor All Information You've Asked for. Deze digitale ontmoetingsplek was aanvankelijk alleen beschikbaar voor AYA's van het Radboudumc, maar werd in 2014 toegankelijk voor alle AYA's in Nederland.

Op dit moment wordt AYA-zorg, onderzoek en onderwijs in Nederland gecoördineerd door de Stichting Nationaal AYA 'Jong & Kanker' Platform (www.aya4net.nl). Deze stichting is in 2016 opgericht en heeft een eigen bestuur. Thans zijn er zes regionale AYA kennisnetwerken verdeeld over Nederland waar de zorg geëchelonneerd wordt aangeboden. Dat wil zeggen dat standaard leeftijdsspecifieke en psychosociale zorg wordt aangeboden door zorgprofessionals van het behandelend naburig ziekenhuis. Indien er echter een indicatie bestaat voor complexe multidisciplinaire AYA-zorg, kan de AYA verwezen worden naar een regionaal AYA kenniscentrum. De leeftijdsspecifieke zorg volgt de medisch-technische zorg. Daarnaast kunnen zorgprofessionals uit heel Nederland de AYA Kenniscentra consulteren.

Doel van dit proefschrift

De onderzoeken beschreven in dit proefschrift zijn grotendeels uitgevoerd onder AYA-patiënten die het AYA-poli zorgteam van het regionaal AYA kenniscentrum Radboudumc in Nijmegen hebben bezocht en onder AYA's uit heel Nederland die gebruik maken van de online AYA community. Het doel van dit proefschrift is om beter inzicht te krijgen in de AYA-doelgroep om de zorg voor hen te verbeteren. Door subgroepen te identificeren die meer risico lopen op bijvoorbeeld psychosociale problemen tijdens en na behandeling, kunnen we de zorg voor deze doelgroep pro-actiever en meer op maat leveren en optimaliseren. Dit proefschrift is onderverdeeld in twee delen. Deel I gaat in op kwaliteit van leven en psychosociale aspecten van kanker op AYA-leeftijd. Deel II gaat in ondersteunende en palliatieve zorg voor AYA's.

Hieronder volgt een overzicht van de belangrijkste resultaten van dit proefschrift. Nadien wordt afgesloten met aanbevelingen voor toekomstig onderzoek en adviezen over hoe de zorg voor AYA's verder verbeterd kan worden.

Deel I: Kwaliteit van leven en psychosociale aspecten bij AYA's

Het meten van kwaliteit van leven vanuit het perspectief van de AYA geeft inzicht in het effect van kanker en de behandeling ervan op fysiek, psychisch en sociaal functioneren.

In Hoofdstuk 2 wordt beschreven welke 10 kwaliteit van leven onderwerpen door AYA's als belangrijkste worden ervaren. Deze top 10 wordt vergeleken met de top 10 die zorgprofessionals, betrokken bij AYA-zorg, aangeven als in hun ogen het meest relevant voor AYA's. Er deden 83 AYA's en 34 zorgprofessionals mee aan dit onderzoek. De belangrijkste onderwerpen voor AYA's met kanker waren ontvangen steun van anderen, angst voor de initiële diagnose van kanker, angst voor de impact op het gezin, de algehele kwaliteit van leven en geluk. Zorgprofessionals gaven aan dat zij angst voor de initiële diagnose van kanker, angst voor de impact op het gezin, vermoeidheid, angst voor de kankerbehandeling, het interfereren van kanker en de behandeling op werk of studie de belangrijkste onderwerpen voor AYA's vonden die hun kwaliteit van leven konden beïnvloeden. De top 10 onderwerpen van AYA's versus die van de zorgprofessionals overlappen elkaar op vijf van de tien items. AYA's scoorden significant lager op negatief geformuleerde kwaliteit van leven items zoals vermoeidheid, problemen met omgaan met kanker en zich geïsoleerd voelen. Zij scoorden significant hoger op positief geformuleerde onderwerpen zoals steun van anderen, algemene fysieke gezondheid en geluk in vergelijking met de zorgprofessionals. Geconcludeerd werd dat AYA's de kwaliteit van leven onderwerpen die het meest negatief geformuleerd waren minder problematisch ervoeren dan zorgprofessionals meenden dat AYA's dat zouden ervaren. De discrepantie in de prioritering van kwaliteit van leven onderwerpen door AYA-patiënten en zorgprofessionals illustreert het belang van patiëntenparticipatie bij de inhoud en de organisatie van AYA specifieke zorg. Het perspectief van de zorgprofessional, dat voornamelijk probleemgericht is, kan worden vergroot door het meenemen van het patiëntenperspectief, wat de leeftijdsspecifieke zorg, en uiteindelijk de kwaliteit van leven van de AYA's, ten goede kan komen.

Hoofdstuk 3 richt zich op het vaststellen van de prevalentie van angst voor terugkeer van kanker bij AYA's en factoren die daarmee geassocieerd zijn zoals kwaliteit van leven, angst en distress. Angst voor terugkeer van kanker is een veel voorkomend probleem bij patiënten met kanker. Eerder onderzoek heeft aangetoond dat een jongere leeftijd geassocieerd is met meer angst voor terugkeer van kanker. Tot op heden was er weinig bekend over hoe angst voor terugkeer zich manifesteert bij AYA's. Door 73 AYA's die het multidisciplinaire AYA-poli zorgteam van het Radboudumc consulteerden, werden vragenlijsten ingevuld over onder andere angst voor terugkeer van kanker, kwaliteit van leven, angst en depressie. Bij 62 % van hen was sprake van een hoge mate van angst voor terugkeer van kanker. Dit was hoger dan gerapporteerd in studies bij volwassen patiënten met kanker. Een hoge mate van angst voor terugkeer van kanker was geassocieerd met lagere niveaus van sociaal en psychisch functioneren en kwaliteit van leven en met meer psychische distress. Deze resultaten illustreren dat angst voor terugkeer van de kanker een belangrijk probleem is bij AYA's. Als aanbeveling wordt meegegeven dat de zorgverlener specifieke aandacht zou moeten besteden aan de mate aan angst voor terugkeer van kanker bijvoorbeeld door systematisch hierop te screenen. Dit kan helpen om de psychosociale zorg daarop gericht aan te passen.

Hoofdstuk 4 beschrijft de prevalentie van ernstige vermoeidheid bij AYA's, de impact die ernstige vermoeidheid heeft en welke factoren hieraan bijdragen. Ernstige vermoeidheid op basis van een gevalideerde afkapwaarde in een vragenlijst kwam voor bij 48% (n=40/83) van de AYA's die de AYA-polikliniek bezochten. Dit percentage is aanzienlijk hoger dan in de algemene populatie waar slechts 20% van de op leeftijd en geslacht gematchte groep ernstig vermoeid is. Dit onderzoek toonde aan dat ernstig vermoeide AYA's een significant lagere kwaliteit van leven rapporteerden op zowel het fysieke, psychologische, sociale als spirituele domein. Ernstige vermoeidheid was geassocieerd met vrouwelijk geslacht, werkloosheid (of niet studerend), vergevorderde kanker bij diagnose, actieve behandeling ten tijde van het invullen van de vragenlijst, palliatieve intentie van de behandeling en eerdere bestraling. Daarnaast lieten de resultaten zien dat hogere vermoeidheidscores geassocieerd waren met angst voor terugkeer van kanker en met psychische distress. De bevindingen van deze studie benadrukken het belang van zorgvuldige aandacht voor vermoeidheid bij AYA's. Op grond van de resultaten is het aan te bevelen met regelmaat te screenen op de aanwezigheid van ernstige vermoeidheid en om behandelbare factoren te identificeren (bijvoorbeeld psychische klachten en slaapstoornissen). Dit geldt voor zowel tijdens als na afloop van de behandeling voor kanker.

Hoofdstuk 5 bevat een literatuuroverzicht over post-traumatische groei en veerkracht bij AYA's met kanker. Kwalitatieve interviewstudies toonden aan dat post-traumatische groei door AYA's beschreven werd in termen van voordelen, waaronder een veranderde kijk op het leven en het zich sterker en zelfverzekerder voelen. Veerkracht werd beschreven als een evenwicht tussen verschillende factoren, waaronder stress en omgaan met kanker, doelen stellen, optimisme, betekenis en zingeving, verbinding maken met anderen en ergens bij horen. Kwantitatief onderzoek toonde aan dat sociodemografische en klinische kenmerken niet geassocieerd waren met post-traumatische groei. Langdurige stress was negatief en sociale steun positief geassocieerd met post-traumatische groei. Angst voor ziekte- en behandelingsgerelateerde symptomen, en een defensieve coping strategie waren negatief geassocieerd met veerkracht. Als er daarentegen sprake was van meer bewust omgaan met ervaringen, de zogenaamde adaptieve cognitieve coping, dan was dit positief geassocieerd met veerkracht. Zowel post-traumatische groei als veerkracht waren positief geassocieerd met tevredenheid met het leven en met kwaliteit van leven. Hoe ten gevolge van ziekte- en behandelingsgerelateerde distress de ervaren kwaliteit van leven bepaald wordt, heeft o.a. te maken met veerkracht. In het review worden twee interventies beschreven die onder andere gericht waren op het bevorderen van veerkracht, namelijk een stress-management interventie en een therapeutische videoclip-interventie. Het bleek dat deze er niet in slaagden de algehele veerkracht te vergroten onder deelnemende AYA's. De meeste AYA's ervoeren slechts een beetje post-traumatische groei of veerkracht. Onderzoek naar factoren die geassocieerd zijn met post-traumatische groei en veerkracht, zoals distress ten gevolge van ziekte en behandelingsgerelateerde symptomen, stress, omgaan met kanker, sociale steun en fysieke activiteit kan bijdragen aan inzicht in welke interventies zinvol en effectief zijn ter verbetering van post-traumatische groei en veerkracht en het uiteindelijk verminderen van negatieve uitkomsten.

Een van de veronderstelde mechanismen om post-traumatische groei en veerkracht te bereiken is empowerment. Empowerment is het vermogen van een persoon zichzelf te versterken om controle te verwerven of behouden over zijn eigen leven. De vragen en problemen die AYA's tegenkomen tijdens en na kanker, kunnen van invloed zijn op de mate van empowerment die zij ervaren. De doelstelling van **hoofdstuk 6** was om de mate van empowerment en daarmee geassocieerde (demografische, klinische of psychologische) factoren te onderzoeken en om het verband tussen empowerment en kwaliteit van leven bij AYA's te onderzoeken. De vragenlijsten werden door 83 AYA's ingevuld. Van hen was 83% behandeld met (onder andere) chemotherapie en had 74% de behandeling voor kanker afgerond. De multivariate analyse toonde aan dat onderdelen van autonomie (zelfbewustzijn, het vermogen om nieuwe situaties te overzien) en sociale steun positief geassocieerd waren met empowerment. Vrouwelijke AYA's scoorden lager op empowerment in vergelijking met mannelijke AYA's. Coping problematiek, oftewel moeite hebben met het omgaan met de ziekte, bleek negatief geassocieerd te zijn met empowerment. Empowerment was onafhankelijk geassocieerd met fysieke, psychologische, sociale, religieus en algemene ervaren kwaliteit van leven. Het herkennen van AYA-patiënten die baat zouden kunnen hebben bij interventies die het doel hebben om de empowerment te vergroten, zou kunnen bijdragen aan de verbetering van hun kwaliteit van leven.

Deel II: ondersteunende en palliatieve zorg

Om te kunnen omgaan met kanker en de gevolgen van de behandeling is het van essentieel belang om de juiste leeftijdsspecifieke zorg op het juiste moment en de juiste plek te kunnen bieden aan elke AYA en diens naaste. In **Hoofdstuk 7** worden het gebruik en de evaluatie beschreven van de online AYA community, een digitale 'hangplek' voor Nederlandse AYA's. De community heet AYA4 en is de afkorting van 'All Information You've Asked for'. Deze community was door AYA's gewenst omdat AYA's aangaven dat het lastig was andere AYA's te ontmoeten. In 2010 werd de community op basis van de wensen van AYA's ontwikkeld en in gebruik genomen. De AYA community werd op uitdrukkelijk verzoek van AYA's alleen toegankelijk gemaakt voor henzelf. Sinds de start van de AYA community in 2010 is het ledental in 2017 uitgegroeid naar 433 waarvan 71% vrouw is. De gemiddelde leeftijd bij diagnose kanker was 25,7 jaar. De leden zijn afkomstig van 52 van de 91 ziekenhuizen in Nederland. Uit een nationaal vragenlijstonderzoek onder 66 AYA's bleek dat 30 van hen de AYA community regelmatig gebruikten. Zij gaven aan dat de community bijdroeg aan het gevoel van erkenning en herkenning (78%), door de verhalen van andere AYA's. Zesenvijftig % gaf aan in de community bij andere AYA's terecht te kunnen voor advies met betrekking tot problemen, 63% ervoer ondersteund te worden door andere leden van de community. Bijna de helft van de respondenten voelde zich minder eenzaam. Slechts 14 AYA's gaven toestemming om hun bijdragen (teksten, discussies) aan de community voor een wetenschappelijke studie anoniem te analyseren. De analyse van de inhoud liet zien dat de meerderheid van de online discussies gingen over het delen van informatie en emotie en het ondersteunen van elkaar daarbij. AYA's missen, gezien de zeldzaamheid van kanker op de AYA leeftijd, vaak de mogelijkheid om elkaar persoonlijk te ontmoeten. De resultaten van de beveiligde Nederlandse online AYA community laten zien dat de community bijdraagt aan de mogelijkheid om met elkaar in contact te komen. AYA's gaven aan dat contact met andere AYA's hen helpt om gevoelens te uiten, om informatie uit te wisselen, om hulp te vragen en te krijgen bij het omgaan met kanker en de gevolgen ervan. Het strekt tot aanbeveling dat zorgprofessionals AYA's attenderen op het bestaan en de voordelen van de community.

Omdat 1 op de 5 AYA's met kanker overlijdt aan de ziekte is het belangrijk om de palliatieve zorg, waarvan terminale zorg een onderdeel is, goed in te richten. In **Hoofdstuk 8** worden de ervaringen van nabestaanden en huisartsen in Nederland met palliatieve zorg voor AYA's in de terminale fase geanalyseerd. Vijftien ouders en negen huisartsen betrokken bij negen overleden AYA's vulden vragenlijsten in en werden respectievelijk telefonisch geïnterviewd. Over het algemeen waren de ouders tevreden met de emotionele zorg die ze zelf ontvingen en de medische zorg die hun kind ontving. De huisartsen waren zeer tevreden over de samenwerking met het palliatieve team. Hiaten werden geïdentificeerd op het gebied van symptoombeheersing, communicatie tussen ziekenhuisprofessionals en ouders, nazorg en de overgang tussen ziekenhuis en huisarts. Dit onderzoek geeft aan dat de zorg, met name in de transitiefase van ziekenhuis naar huisarts verbeterd kan worden en dat er specifieke punten voor verbetering liggen.

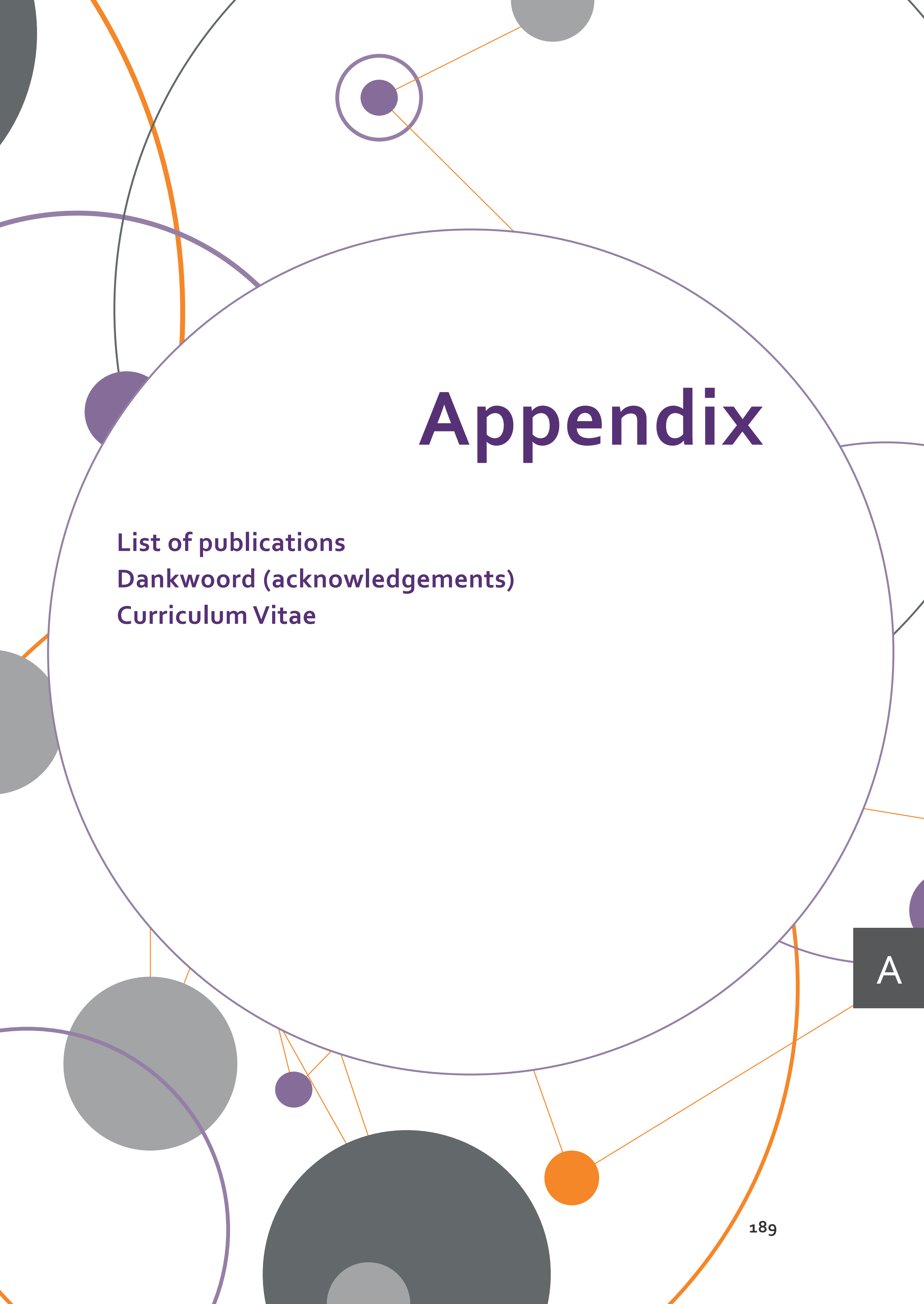
In **Hoofdstuk 9** worden de praktische implicaties van de bevindingen beschreven en aanbevelingen voor toekomstig onderzoek voorgesteld. Dit proefschrift heeft belangrijke inzichten opgeleverd omtrent kwaliteit van leven van AYA's. Het heeft de 10 meest belangrijke kwaliteit van leven items getoond onder AYA's die belangrijk verschilden van de top 10 die zorgprofessionals voor hen in gedachten hadden. Moeheid en angst voor terugkeer van kanker zijn belangrijke elementen die de kwaliteit van leven van AYA's kunnen beïnvloeden. Gelukkig bestaan er ook positieve uitkomsten van patiënten die op AYA-leeftijd kanker krijgen zoals post-traumatische groei en veerkracht. Deze positieve uitkomsten hangen samen met empowerment, een gevoel van controle hebben over het eigen leven. Omdat empowerment geassocieerd is met kwaliteit van leven, is het zaak om interventies te ontwikkelen om empowerment te vergroten. Tevens heeft dit proefschrift laten zien dat de online AYA community een nuttige digitale tool is waar AYA's met elkaar in contact kunnen komen om informatie, emoties en ervaringen uit te wisselen. Toekomstig onderzoek dient zich te richten op de vraag welke AYA's het meeste voordeel hebben van het gebruik van de community, hoe de community uitgebreid dient te worden en de toegevoegde waarde van de inhoudsanalyse van de community. Met betrekking tot terminale zorg voor AYA's is er nog verbetering wenselijk op het gebied van de transitie en communicatie van ziekenhuis naar thuissituatie en symptoomcontrole.

In de nabije toekomst zullen we ons verder richten op het verzamelen van meer data in een grotere AYA-populatie afkomstig uit meer ziekenhuizen in Nederland. De infrastructuur van het Nationaal AYA 'Jong & Kanker' Platform maakt grootschalig onderzoek en educatie van zorgprofessionals gemakkelijker. Daarnaast is het zinvol om (online) interventies te ontwikkelen voor AYA's om enerzijds persoonlijke kracht te vergroten en anderzijds vermoeidheid en angst voor terugkeer van kanker te verminderen. Het is van belang dat AYA-zorg in de toekomst wordt geëvalueerd in termen van patiënttevredenheid, kwaliteit van leven, overleving en deelname aan klinische studies. Daarbij kunnen nieuwe, robuuste eindpunten, zoals bijvoorbeeld minder zorgconsumptie voor psychosociale problemen en een snellere terugkeer naar werk, behulpzaam zijn om de effectiviteit van AYA-zorg aan te tonen.

Figuur 1: Leeftijdsspecifieke aspecten bij AYA's met kanker

Concluderend

AYA's met kanker vormen een aparte groep met unieke medische en psychosociale zorgbehoeften. Zorgprofessionals dienen meer zicht te krijgen in factoren die specifiek zijn voor de AYA-populatie om zowel de leeftijdsspecifieke ondersteunende zorg als de medische zorg te verbeteren. Het is van groot belang om te bepalen welke AYA-patiënten meer risico hebben op psychosociale problemen en dus baat kunnen hebben bij (online) interventies. De laatste jaren is er grote vooruitgang geboekt op het gebied van AYA zorg, onderzoek en onderwijs, onder andere door de oprichting van de Stichting Nationaal AYA 'Jong & Kanker' Platform. Helaas bestaat er nog geen structurele financiering voor deze zorg. De Stichting Oncologische Samenwerking (SONCOS), het platform voor interdisciplinair overleg en professionele samenwerking in de oncologische zorg tussen beroepsverenigingen, heeft het belang van leeftijdsspecifieke AYA-zorg onderkend. Omdat AYA-zorg inmiddels is opgenomen in het SONCOS normeringsrapport, wordt deze zorg minder vrijblijvend en kan er in de toekomst ook op getoetst worden. Dit proefschrift is een aanzet om te komen tot proactieve psychosociale AYA-zorg op maat waarbij verder onderzoek zal uitwijzen of dit leidt tot betere uitkomsten in de kwaliteit van leven van AYA's.



Appendix

List of publications
Dankwoord (acknowledgements)
Curriculum Vitae

List of Publications

1. Casali PG, Abecassis N, Bauer S, Biagini R, Bielack S, Bonvalot S, Boukovinas I, Bovee JVMG, Brodowicz T, Broto JM, Buonadonna A, De Álava E, Dei Tos AP, Del Muro XG, Dileo P, Eriksson M, Fedenko A, Ferraresi V, Ferrari A, Ferrari S, Frezza AM, Gasperoni S, Gelderblom H, Gil T, Grignani G, Gronchi A, Hannu A, Hassan B, Hohenberger P, Issels R, Joensuu H, Jones RL, Judson I, Jutte P, **Kaal S,** Kasper B, Kopeckova K, Krákorová DA, Le Cesne A, Lugowska I, Merimsky O, Montemurro M, Pantaleo MA, Piana R, Picci P, Piperno-Neumann S, Pousa AL, Reichardt P, Robinson MH, Rutkovski P, Safwat AA, Schöffski P, Sleijfer S, Stacchiotti S, Sundby Hall K, Unk M, Van Coevorden F, Van der Graaf W, Whelan J, Wardelmann E, Zaikova O, Blay JY; ESMO Guidelines Committee and EURACAN. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 May 28.

2. Casali PG, Abecassis N, Bauer S, Biagini R, Bielack S, Bonvalot S, Boukovinas I, Bovee JVMG, Brodowicz T, Broto JM, Buonadonna A, De Álava E, Dei Tos AP, Del Muro XG, Dileo P, Eriksson M, Fedenko A, Ferraresi V, Ferrari A, Ferrari S, Frezza AM, Gasperoni S, Gelderblom H, Gil T, Grignani G, Gronchi A, Hannu A, Hassan B, Hohenberger P, Issels R, Joensuu H, Jones RL, Judson I, Jutte P, **Kaal S,** Kasper B, Kopeckova K, Krákorová DA, Le Cesne A, Lugowska I, Merimsky O, Montemurro M, Pantaleo MA, Piana R, Picci P, Piperno-Neumann S, Pousa AL, Reichardt P, Robinson MH, Rutkovski P, Safwat AA, Schöffski P, Sleijfer S, Stacchiotti S, Sundby Hall K, Unk M, Van Coevorden F, Van der Graaf W, Whelan J, Wardelmann E, Zaikova O, Blay JY; ESMO Guidelines Committee and EURACAN. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. 1. Ann Oncol. 2018 May 28.

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Dankwoord

Mijn boekje is af! Maar mijn werk in 'AYA-land' is nog niet klaar. Toch sluit ik, met gepaste trots, een belangrijke periode af. Een periode van leren, groeien, doorzetten, groot worden en soms (een beetje) worstelen. Het overkoepelende werkwoord voor dit alles is promoveren. Onderstaande personen hebben op enigerlei wijze bijgedragen aan de totstandkoming van dit proefschrift en wil ik daarom graag bedanken.

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Een proefschrift volbrengen in combinatie met de taken van medisch-specialist lukt alleen met de steun van een getraind elftal met een solide basis, namelijk de afdeling Medische Oncologie. Een aantal spelers wil ik graag bij naam noemen. Prof. dr. ir. J.J.M. van der Hoeven, beste Koos, als aanvoerder (afdelingshoofd) heb je mij altijd gefaciliteerd en gesteund. Op de juiste momenten gaf je me een duwtje in de rug. Dank daarvoor. Drs. ing. Erik Lambeck, beste Erik, jouw tactisch inzicht is groot, jouw financieel inzicht nog groter en als spelverdeler weet jij ook wat er ècht gebeurt in de spreekkamer. Stafleden medische oncologie, jullie zijn een mooie, diverse club internist-oncologen met overlappende eigenschappen: zorgzaam, ambitieus en (prettig) eigenwijs. Jullie vormen de basis van het team. Ik kijk er naar uit die basis de komende jaren verder uit te bouwen. Prof. dr. Carla van Herpen, beste Carla, kamergenoot, wat krijg jij veel voor elkaar! Ondanks je drukke agenda maak je altijd tijd vrij om te informeren hoe het met me gaat. Dr. Sasja Mulder, ballenmaatje, met jou kan ik heerlijk lachen en stoom afblazen. Bijna (!) dr. Evelien Kuip, ik kijk er naar uit om jou te zien stralen bij de verdediging van jouw proefschrift. Collega's van de afdeling medisch oncologie, fellows, arts-onderzoekers, verpleging, research, secretariaat en overige collega's. Met velen van jullie deel ik al ruim 10 jaar de Nijmeegse werkvloer. Het hoge arbeidsethos, de goede onderlinge sfeer en betrokkenheid maakt dat ik elke dag met plezier naar mijn werk ga. En dat is veel waard! Dank daarvoor.

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Lieve vriendinnen en vrienden. Jullie zijn me heel dierbaar. Ik koester onze momenten van samenzijn, de latte macchiato’s, wijntjes, etentjes, tripjes, shop till you drop dagen, saunabezoeken en nog veel meer. Ook in moeilijkere tijden waren jullie er altijd voor mij en dat heb ik zeer gewaardeerd. Bijzondere dank aan de helpdesk-vriendinnen die in de eindspurt hebben bijgedragen aan het controleren van de inhoud van dit proefschrift.

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Curriculum Vitae

Suzanne Elisabeth Jacqueline Kaal werd geboren op 11 mei 1977 in Venlo. In 1995 behaalde zij haar VWO-gymnasium diploma aan het St. Thomascollege te Venlo. Datzelfde jaar begon zij aan de opleiding Biomedische Gezondheidswetenschappen aan de Katholieke Universiteit Nijmegen (thans: Radboud Universiteit) met hoofdvak pathobiologie en bijvak geneesmiddelenonderzoek. In 1999 behaalde zij haar doctoraal examen en startte zij met de opleiding Geneeskunde aan dezelfde universiteit. In 2003 behaalde zij haar artsexamen waarna zij werd aangenomen voor de opleiding Interne Geneeskunde onder supervisie van aanvankelijk prof. dr J.W.M. van der Meer en later prof. dr. J. de Graaf. Van 2003 tot 2007 werkte zij als AIOS Interne Geneeskunde in het St Elisabeth Ziekenhuis te Tilburg (thans ElisabethTweeSteden Ziekenhuis) onder leiding van dr C. van der Heul en dr. P.L. Rensma. Daarna zette zij haar opleiding voort in het Radboudumc, aanvankelijk op de afdeling hematologie. In 2008 startte zij haar differentiatie Medische Oncologie met als opleider Prof dr W.T.A. van der Graaf. In 2009 rondde zij haar opleiding tot internist-oncoloog af. Sinds 2010 is zij verbonden als staflid aan de afdeling medische oncologie van het Radboudumc met als aandachtsgebieden zorg voor jongvolwassenen met kanker (AYA's: Adolescents and Young Adults), bot en weke delen tumoren en zaadbalkanker. Vanaf die periode heeft zij een bijdrage geleverd aan de opzet en uitrol van AYA-zorg in het Radboudumc en daarbuiten. Zij is projectleider AYA-zorg van het Radboudumc en de regio Midden-Oost. Suzanne is de trotse moeder van Okke (2009) en Lola (2012).