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SPECIAL ARTICLE

Management of late toxicities and specific follow-up needs of adolescent and young adult cancer survivors: recommendations from scientific societies in Spain

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Abstract

Adolescent and young adult cancer survivors (AYACS) represent a specific cancer patient population with unique chronic health issues difficult to identify in early, reversible phases with standard monitoring protocols. This review, conducted by a group of Spanish experts, provides recommendations for managing AYACS, focusing on key areas, such as cardiac toxicities, neurotoxicity and neurocognitive disorders, metabolic syndrome, secondary primary malignancies, bone toxicities, sexuality and fertility, psychosocial aspects, and other treatment-related toxicities.

Keywords Adolescent · Cancer · Recommendations · Survivors · Toxicity · Young adult

Introduction

The adolescent and young adult (AYA) age group, defined hereby as the period from 15 to 39 years, constitutes a specific group with multiple challenges in the prevention, diagnosis, treatment (including management of toxicities), and long-term sequelae of cancer [1]. Due to the constant improvement in the effectiveness of treatments and increased survival, the number of long-term AYA cancer survivors (AYACS) is increasing, with a growing population of 100,000 cases per year in Spain. In 2020, AYA cancer represented 5% of the total new cancers diagnosed in Europe [2]. Although the 5 year survival rate in AYAs in the United States (US) was similar for all cancer types combined (approximately 85%), there was notable variation when AYAs were subdivided into younger and older subgroups [3]. For example, 5 year survival rates after lymphocytic leukemias were 74% in adolescents aged between 15 and 19 years versus 52% in patients aged 20–29 and 51% in individuals aged 30–39 years; similar distribution patterns were observed for brain/other nervous system tumors [3]. Importantly, within the AYA age group, differences in cancer types, survival, toxicities, and overall impact should be highlighted between those aged 15–19, 20–29, and 30–39 years, and carefully considered when applying recommendations [3].

Since AYACS may present with problems specific to their age group that are not always easily recognized by clinicians or easily managed, there is a need to establish guidelines for their long-term follow-up (with the highest impact in breast, thyroid, testicle cancer, lymphoma, and leukemia) [1, 4, 5]. Priorities that should be addressed in these guidelines include describing hereditary tumors, incorporating AYACS in clinical trials, integrating them into the workforce, evaluating long-term consequences, such as late-onset toxicities

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or conditions—particularly those affecting sexual and reproductive function. Additionally, the potentially greater psychological and emotional impact of cancer in AYACS compared to older adults should be carefully considered [1, 5]. The impact of late sequelae on health-related quality of life (HRQoL) can be significant in the AYA age group, given their high level of activity and personal or professional development relative to other age groups [1]. Healthcare practitioners' familiarity with the specific patterns of treatment-related late-onset toxicities (eg, on the cardiovascular, nervous, or endocrine systems) and the extent of involvement of these systems may enhance the quality of long-term follow-up of AYACS and could impact the successful maturing of adolescents into adulthood [6, 7].

Therefore, a group of Spanish experts met in 2023 to develop a series of practical recommendations to assist health professionals and institutions in establishing recommendations for the follow-up of late toxicities and long-term management of the specific needs of AYA survivors of childhood cancer.

Methods

The multidisciplinary expert meeting included members from six scientific societies in Spain: the Spanish Society of: Radiation Oncology (SEOR), Pediatric Hematology and Oncology (SEHOP), Medical Oncology (SEOM), Primary Care Physicians (SEMERGEN), General and Family Physicians (SEMG), and Hematology and Hemotherapy (SEHH). One or more representative authors from each scientific society developed key messages and recommendations based on their expertise in their respective fields on the following topics: (*a*) epidemiology of cancer in AYACS; (*b*) cardiac toxicities; (*c*) neurotoxicity and neurocognitive disorders; (*d*) metabolic syndrome; (*e*) secondary primary malignancies; (*f*) bone toxicities; (*g*) sexuality and fertility; (*h*) psychosocial aspects and challenges; and (*i*) other toxicities.

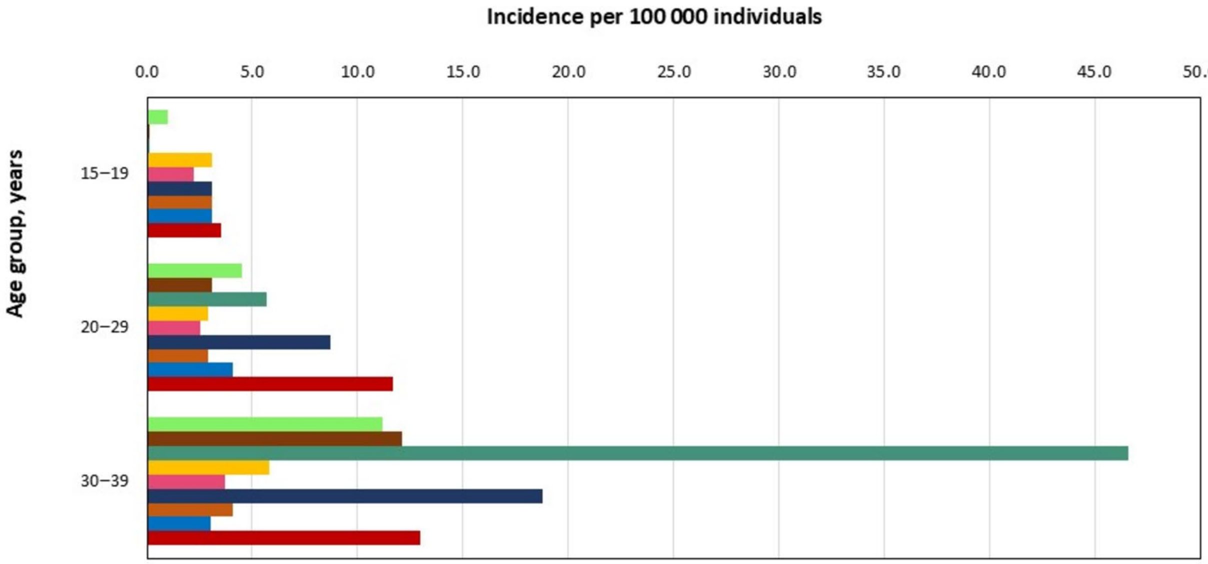
We adhered to the international guidelines and the European and US oncology societies (European Society of Medical Oncology [ESMO] and the US National Cancer Institute) to define the AYA age range as 15–39 years. We considered the 0–14 age group as childhood, according to its generally accepted definition [8], although in Spain, the pediatric age is considered to be until 18 years from a legal viewpoint.

Epidemiology of cancer in adolescents and young adults

The incidence of cancer is at least four times greater in those aged 15–39 years than in those aged 0–14 years [9], and the annual incidence of cancer in this age group increased globally between 2007 and 2016 [3]. According to Globocan 2022 data, the worldwide incidence of cancer in individuals aged 15–39 years was 41.0 cases per 100,000 individuals, most commonly affecting the breast (incidence of 14.9 cases per 100,000 individuals), thyroid, and cervix [10]. The total incidence of non-Hodgkin lymphoma (NHL) (1.6 cases per 100,000 individuals) and leukemia (2.2 cases per 100 000 individuals) indicates that hematological neoplasms are another significant entity in this population [11, 12]. In Europe, the Cancer in AYA Working Group reported in 2020 that there were approximately 112,000 new cases during that year of cancer in AYA, with wide variation between individual countries (eg., 51.0–58.3 cases per 100,000 individuals in Spain, 58.3–63.9 per 100,000 in Germany and UK, and ≥ 63.9 per 100,000 in France and Italy [2]). In the Netherlands, the incidence of AYA cancers increased significantly from 54.6 in 1990–1999 to 70.3 per 100,000 person-years in 2010–2016 [13]. In the US, the incidence of cancer in AYAs between 2014 and 2018 was 77.9 cases per 100,000 individuals [14], and in 2020, the estimated number of new cancer cases in this age group was 89,500 [3]. In Japan, national registry data indicate that 20,000 new cases of cancer are diagnosed annually in AYAs [15].

When the AYA group was subdivided further, the 15–19 years-old group experienced testicular, Hodgkin lymphoma (the most common in those 15–25 years old), leukemia, thyroid, brain and other nervous systems, and NHL cancers most frequently (Fig. 1) [3]. When comparing the 15–19 years group with the 20–29 years group, all of the abovementioned cancers (except leukemia) were more common in the older group, while in the 30–39 years age group, breast, thyroid, testicular, uterine cervix tumors, and melanoma represented the most frequent cancer types [3].

There were 12,700 cancer deaths in AYAs in the European Union in 2018 [9], while the incidence of cancer mortality in the US between 2015 and 2019 was 8.8 deaths per 100,000 individuals [14]. In Spain, there is a relatively low incidence of cancer mortality in the AYA group (< 5 deaths per 100,000), notable given that cancer in this group occurs with an incidence of 51.0–58.3 cases per 100,000 [2]. In this sense, cancer mortality rates and 5 years cancer survival probabilities have been increasing in AYACS, with similar trends reported in younger pediatric and older adult age groups [15]. However, survival in the AYA group is generally lower than in the childhood age group and in adults > 40 years old due to differences in tumor biology, treatment adherence, lower participation in clinical trials, and greater treatment toxicity [1]. In addition, this group has unique social, emotional, fertility, and academic needs [15], which makes improving the survival and HRQoL of this age group challenging for healthcare systems [16]. Notably, the economic repercussions of cancer in AYAs are high for



	30–39	20–29	15–19
■ Melanoma	11.2	4.5	1.0
■ Uterine cervix	12.1	3.1	0.1
■ Breast	46.6	5.7	0.1
■ Non-Hodgkin lymphoma	5.8	2.9	3.1
■ Brain and ONS	3.7	2.5	2.2
■ Thyroid	18.8	8.7	3.1
■ Leukemia	4.1	2.9	3.1
■ Hodgkin lymphoma	3.0	4.1	3.1
■ Testicular	13.0	11.7	3.5

Fig. 1 Incidence of cancer (by site) most frequently experienced by adolescents and young adults between 2012 and 2016 [3]. Abbreviations: ONS, other nervous system

any country because of higher healthcare costs and loss of productivity [17].

The spanish registry of childhood tumors (RETI-SEHOP)

In 2016, the Spanish Ministry of Health officially recognized the RETI-SEHOP as a National Health System registry, confirming it as a reliable source of data for generating health statistics in Spain [18]. The RETI-SEHOP provides essential information on Childhood cancer in Spain, having captured 95% of its incidence in children (0–14 years) since 1980. However, once patients turn 15, coverage decreases, and underreporting and report incompleteness increase, and, thus, also the entry of their medical information into RETI-SEHOP, resulting in a lack of information on cancer in the younger age range of AYA (15–19 years) [18, 19]. Although approximately 500 new cancer diagnoses are expected per year in adolescents (15–19 years), RETI-SEHOP has only reported 1379 new notifications in 13 years (2010–2023) [19]. The adolescent population in Spain is only partially covered by other registries, such as the REDECAN network (14 consolidated registries covering approximately 13 million individuals, representing 27% of the Spanish population of all ages) [20].

Late toxicities in AYACS: recommendations

Cardiac toxicities

Cardiovascular toxicity is one of the most relevant late toxicities in AYACS. They can range from asymptomatic processes to severe and fatal outcomes, occurring not only during the period of active treatment but also during the later years, and they are more frequent in patients < 35 years [21, 22].

AYACS should be classified according to the risk of developing cardiac toxicity as follows:

(a) High-risk patients: Patients should be considered high risk for cardiac toxicity if: (1) They have developed any new cardiac symptoms or moderate-to-severe cardiovascular toxicity during treatment, even if the toxicity has been resolved; or (2) in case of asymptomatic patients in one of the following situations:

a. Total cumulative doxorubicin dose 250–399 mg/m.[2]
b. Radiotherapy (RT) > 15–25 Gy mean heart dose
c. RT > 5 Gy mean heart dose and doxorubicin ≥ 100 mg/m.[2]
d. High-risk hematopoietic stem cell transplant (HSCT), including patients who have received ≥ 250 mg/m^2 of doxorubicin (or equivalent), those treated with mediastinal or mantle field radiation, allogeneic HSCT recipients, those treated with high-risk conditioning regimens (eg, total body irradiation, alkylating agents), or those who develop graft versus host disease (GVHD).

(b) Very-high-risk patients: Patients should be classified as very high risk if one of the following occurs:

a. RT > 25 Gy mean heart dose or RT ≥ 35 Gy to a volume exposing the heart if the mean heart dose is not available
b. Total cumulative doxorubicin dose ≥ 400 mg/m.[2]
c. RT > 15 Gy mean heart dose and doxorubicin dose ≥ 100 mg/m.[2]

Cardiological surveillance during the follow-up of AYACS is necessary because treatment-related cardiovascular disease (CVD) is associated with a high risk of morbidity and mortality [23]. The reported proportion of patients with cancer therapy-related cardiac dysfunction has been shown to increase significantly from 1.64 to 11.72% when cardiac function is screened actively at the end of treatment, which suggests that CVD in this population is widely underdiagnosed [24]. Indeed, among cancer survivors, around 26% had been estimated to have underdiagnosed CVD risk factors (21% undertreated) [25]. A long follow-up study revealed that, 25 years after cancer diagnosis, the health-related causes of death exceeded cancer recurrence. AYACS were 4.2 times more likely to die from CVD than the general population [26]. Besides, a small group of very-high-risk AYACS have around 10% cumulative incidence of heart failure or ischemic heart disease [27], and up to 30% will exhibit subclinical changes in their cardiac function [28]. Excess deaths of 138 per 10,000 survivors-years of follow-up beyond 40 years from cancer diagnosis have been reported, and most of these deaths were attributable to health-related causes, including also those from late effects of cancer treatment [29]. The prevention and control of CVD risk factors (hypertension, diabetes, dyslipidemia) and promotion of a healthy lifestyle in AYACS would reduce late mortality risk [29]. As recommended in other guidelines, toxicity risk should be stratified before and after cancer treatment [30]. Ten years after cancer diagnosis, a mid-range left ventricular ejection fraction (40–49%) has been associated with an eightfold increase in risk for left ventricular dysfunction with an ejection fraction < 40% compared with those with a preserved ejection fraction (≥ 50%) [31]. In this context, N-terminal pro–B-type natriuretic peptide (NTproBNP) has been identified as a promising prognostic marker for ruling out left ventricular dysfunction in adult survivors of childhood cancer [32]. Furthermore, carvedilol may be a promising treatment for reducing heart failure risk in AYACS with elevated NTproBNP [33, 34].

Hypertension

The incidence of hypertension secondary to cancer treatment in AYACS is two or three times higher than in the general population. In this subgroup, elevated blood pressure (BP) has been linked to both genetic predisposition and risk factors such as abdominal or thoracic radiotherapy, corticosteroid use, vascular damage, and renal fibrosis [35, 36].

Recommendations for heart failure prevention and cardiovascular risk optimization, aligned with the 2022 ESC Cardio-Oncology Guidelines [30]

- Inform, advise, and support AYACS in adopting a healthy lifestyle and engaging in regular physical activity to prevent late cardiovascular complications.
- Refer AYACS to a cardiology or cardio-oncology clinic if new cardiovascular signs or symptoms are identified during routine cardiovascular risk assessments by primary care providers.
- Annual cardiovascular risk assessment, including clinical evaluation, BP measurement, lipid profile, glycated hemoglobin (HbA1c), and serum B-type natriuretic peptide (BNP or NT-proBNP), is recommended in AYACS.
- AYACS should be classified according to risk for future cardiac toxicity.
- In high- or very-high-risk AYACS, perform an annual electrocardiogram during the first 5 years after cancer treatment and every 5 years thereafter.
- In AYACS treated with anthracyclines, perform echocardiography 1 year after treatment completion.
- In AYACS at high or very high risk of cancer therapy-related cardiac dysfunction (based on the type of treatment received), follow-up echocardiography should be considered 3 and 5 years after completion of therapy.
- AYACS who develop moderate-to-severe cardiovascular toxicities during cancer treatment should be considered high-risk patients and require annual cardiovascular risk assessment.

Neurotoxicity and neurocognitive disorders

Neurocognitive sequelae may occur as a result of RT or chemotherapy and can significantly decrease HRQoL in AYACS [37] because of their effects on various cognitive domains (processing speed, attention, learning and memory, and executive functioning) [7, 37–39]. Younger age at treatment, intrathecal chemotherapy, certain types of intravenous chemotherapy, and cranial irradiation are associated with poorer neurocognitive outcomes (eg, general intellectual abilities, academic functioning, and specific cognitive abilities) [40–42]. If left untreated, these deficits persist into adulthood [43] and may lead to difficulties in academic training and securing employment [43, 44]. Factors directly linked to the risk and severity of long-term neurocognitive effects from cranial irradiation include patient age at the time of RT, localized versus craniospinal irradiation, type of technique used (protons vs. photons), and the doses received [45]. Focal proton techniques are associated with a lower incidence of neurocognitive effects and offer greater protection of healthy brain tissue adjacent to the treatment area [45]. Treatment with antineoplastic agents, such as cisplatin, can cause sensory neuropathies, numbness, and tingling in the extremities, while taxanes can cause paresthesia and pain in the extremities [46].

Recommendations

- Post-treatment neuropsychological evaluation (for neurocognitive damage and motor disturbances) is highly recommended 6 months after treatment and then every year for at least 5 years in patients receiving cranial irradiation or with risk factors for neurocognitive damage.
- When administering cranial irradiation treatment, radiotherapists should be aware of potential neurologic damage and consider patient age, dose received, the use of localized versus craniospinal irradiation, and the fact that proton RT could be preferred over photon therapy.
- Monitor AYACS for ischemic events after RT.

Metabolic syndrome

Metabolic syndrome comprises a group of symptoms, including insulin resistance, hyperinsulinemia, glucose intolerance, elevated triglycerides (TG), a reduced level of high-density lipoprotein cholesterol (HDL-C), obesity, and hypertension. Childhood and AYA cancer survivors have an increased risk of developing CVD and type 2 diabetes mellitus (T2DM) [47]. The probability of survival of AYACS with metabolic syndrome is influenced by the type of RT (cranial, abdominal, or total body), systemic therapy (chemotherapy, new targeted treatments, such as TKIs or steroids), or surgery they received [48].

Obesity

Young cancer survivors have an increased risk for obesity [36]. Cranial RT can also contribute to the development of obesity through its effects on the hypothalamus and pituitary gland, with subsequent effects on hormones related to appetite, metabolism, and body fat distribution [47, 49]. Leptin resistance can occur as a result of mutations in the genes encoding leptin and its receptors or dysfunction of proteins involved in the regulation of leptin synthesis and the transport of leptin across the blood–brain barrier [50]. This resistance leads to secondary leptin elevation in the blood (resulting in an increased body mass index [BMI], glucose intolerance, insulin resistance, and visceral adiposity) [51]. Hormonal treatments (tamoxifen, luteinizing hormone-releasing hormone analogs, etc.) and hormonal dysfunction secondary to treatment with TKIs, busulfan, or cyclophosphamide may also contribute to obesity [52]. Vitamin D deficiencies may arise because of its distribution into fat tissue, poor nutrition, decreased sun exposure, and a sedentary lifestyle [53]. Other factors that can raise BMI include cancer at an early age, Hispanic ethnicity, genetic predisposition, specific cancer types (acute lymphoblastic leukemia [ALL], central nervous system [CNS] tumors), and untreated hormone deficiencies [35].

Dyslipidemia

Dyslipidemia is defined by increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and TG levels, and decreases in HDL-C levels [54]. AYACS may develop dyslipidemia for different reasons: untreated hypogonadism or growth hormone deficiency, treatment with platinum agents, HSCT, and obesity [36, 55].

Type 2 diabetes mellitus and insulin resistance

The main factor contributing to T2DM and insulin resistance in cancer is abdominal RT, which can cause subcutaneous adipose tissue dysfunction, lipid accumulation, and visceral and free fatty acid circulation with hepatic steatosis [53, 55]. Systemic cancer treatments, such as corticosteroids, some cytostatic agents (platinum, L-asparaginase), and targeted treatments (insulin growth factor receptor 1 inhibitors and mammalian target of rapamycin inhibitors), can increase the risk of insulin resistance and T2DM via increased gluconeogenesis, β-cell toxicity (decreased insulin production), cytokine release, chronic inflammation, reduction of insulin receptor levels, and hyperglycemia [36, 53].

Recommendations

- Early detection of metabolic syndrome, long-term screening, monitoring, and individualized treatment of all AYACS at risk or presenting with any symptoms of metabolic syndrome is recommended.
- Analysis, including at least glucose, total cholesterol, LDL-C, and TG levels, as well as decreases in HDL-C levels, should be performed yearly.
- Patients with mild-to-moderate risk of toxicities should be followed up for 10 years, and those with high risk for at least 15 years but indefinite follow-up can be considered if diagnosis was in younger age.
- Encourage AYACS to adhere to treatment goals (Table 1) and to attend annual follow-up visits.
- Provide the patient with counseling and education on the importance of healthy living, including engagement in regular physical activity, how to prevent obesity (eg, a balanced caloric intake), early pharmacotherapy, and cessation of smoking or other toxic habits.
- Conduct a baseline evaluation of lipid, HbA1c, and vitamin D levels in the post-treatment phase, and then review annually.
- If cranial RT was received, include an annual assessment of height, weight, and nutritional status; in the case of abdominal RT or total body irradiation, lipid levels and HbA1c should be measured at least every 2 years.
- AYACS with a family history of T2DM should be monitored more closely and specifically; in cases where HbA1c may be less sensitive (such as after HSCT) and insulin resistance is suspected, oral glucose overload testing may be more appropriate.
- Use serum HDL-C and adiponectin levels as lipid markers because of the unfavorable high levels of TG, LDL-C, apolipoprotein B, and uric acid.
- The lipid level and glycemic goals of the rest of the population should also be applied to AYACS (Table 1).

Table 1 Therapeutic goals for the management of metabolic syndrome in AYACS [56]

Variables	Target
Total cholesterol	< 200 mg/dL
LDL-C	< 100 mg/dL
Non-HDL-C	> 131 mg/dL
TG	< 150 mg/dL
BP	< 130/80 mmHg
BMI	< 25 kg/m^2

AYACS, adolescent and young adult cancer survivors; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides

Second primary malignancies

In AYACS, the risk of developing treatment-related second primary malignancies (SPMs) (Table 2) is high due to their increased innate susceptibility to tumor growth (determined by genetic factors), exposure to genotoxic therapy during critical stages of development (such as puberty), and prolonged life expectancy [57]. An SPM incidence of > 20% has been reported up to 30 years after diagnosis of the primary tumor. In the US, there is a 14% higher incidence of SPMs in cancer survivors when compared with the general population (representing the third most common tumor diagnosis among cancer survivors) [57]. High cumulative doses or even low peripheral doses of external beam RT (EBRT) are an established risk factor for SPMs and may lead to a risk of mortality in pediatric and adolescent patients that is up to 10 times higher than in adults [57]. The most frequent SPMs in AYACS are CNS tumors (26.3%), leukemias (23.5%), lymphomas (13.5%), soft tissue sarcomas (8.7%), bone tumors (6.7%), retinoblastomas (5.0%), and renal tumors (3.5%) [57].

RT-related SPM is characterized by (i) SPM arising in the irradiated field, (ii) a latency time between irradiation and SPM development, (iii) divergent histology in relation to the primary tumor, and (iv) development from normal tissue. EBRT or multiagent chemotherapy increases the RT-related SPM risk about sixfold compared to the general population [57]. The appearance of these SPMs depends on the dose, area, irradiated site, and administration with concurrent chemotherapy. Newer RT technologies, including improved image-control technology, have reduced the incidence of SPMs and drastically reduced the amount of irradiated healthy tissue. The more frequent use of lower-dose and precise dose-delivery of proton therapy to treat children and adolescents is recommended to preserve healthy tissue. EBRT, in combination with alkylators and anthracyclines, raises the risk of SPMs involving the breast, lung, stomach, pancreas, thyroid, colon/rectum, and/or soft tissue [57].

The use of alkylating agents and etoposide to treat acute myeloid leukemia (AML), ALL, chronic myelogenous leukemia (CML), and myelodysplastic syndrome (MDS) is associated with an increased risk of chemotherapy-related SPMs [57]. These SPMs typically develop between 2 and 4 years after the start of treatment, and their incidence peaks after 5–9 years [57]. Treating chemotherapy-induced leukemias is challenging because cure rates only reach 10–20%, and genetic alterations occur in differing leukemia subtypes [57].

To alleviate the development of SPMs, referral channels and rapid communication between primary care facilities and hospitals should be established in the event of any sign

Table 2 Secondary tumors common in AYACS

Cancer/tumor type	Causes/risk factors	Additional notes
AML, MDS	Causative agents: classical alkylators (busulfan, carmustine, chlorambucil, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine, thiotepa); heavy metals (carboplatin, cisplatin); non-classical alkylators (dacarbazine and temozolomide); anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone); and epipodophyllotoxins (etoposide, teniposide) [58]	
Bladder cancer	Causative agents: alkylating agents (cyclophosphamide) Contributing factors: pelvic RT; alcohol use; tobacco use [59]	Symptoms: hematuria, urgency or urinary frequency, urinary incontinence, dysuria, nocturia, and/or abnormal urine flow
NHL	Risk factors: prior chemotherapy treatment, primary cancer type (Wilms tumor, Hodgkin lymphoma, leukemias, and bone sarcomas) [60]	Prior chemotherapy treatment; previous RT does not increase the risk of secondary NHL [60]
Breast cancer and lymphedema	Causative agents: RT of primary tumor (of the breast or chest), high-dose irradiation of the external axillary or inguinal nodes, lymph node removal (in pelvic cancer, lymphoma, melanoma, and head and neck cancer) Risk factors: use of anthracyclines when the adjusted doxorubicin dose ≥ 250 mg/m^2; smoking [61]	In women unexposed to chest radiation, the cumulative incidence of breast cancer was 1% at 35 years of age; however, after exposure to ≥ 10 Gy, incidence rates rose to 8% at 35 years of age [62] AYACS who had received ≥ 10 Gy of chest radiation during childhood required regular monitoring for breast cancer [62]
CNS tumors	Cranial irradiation is a known risk factor for AYACS to develop CNS neoplasms [63]. Additional risk factors for CNS neoplasms: (i) high doses of radiation and younger age at treatment most commonly cause gliomas (ii) high doses of radiation, younger age at treatment, intrathecal methotrexate and platinum agents cause meningiomas [58, 63]	
Thyroid cancer	Causes: RT, radioactive iodine, and the use of alkylating agents in irradiated patients	Occur in up to 33% of AYAs and are one of the most serious risk factors for decreased overall survival rate compared with those of patients with primary thyroid cancers [64]
Soft tissue sarcomas	High-risk or radio-induced sarcomas after previous radiotherapy. Other risk factors include tobacco and alcohol consumption [58]	
Bone sarcomas	Increased risk of osteosarcoma and, less frequently, Ewing's sarcoma if the primary tumor was retinoblastoma, bone sarcomas, or soft tissue sarcomas [4, 65]	

AML, acute myeloid leukemia; AYACS, adolescent and young adult cancer survivors; CNS, central nervous system; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; RT, radiation therapy or symptom of suspicion, relapse, the appearance of a new late toxicity, or an SPM [49].

Recommendations

- AML or MDS: conduct blood analysis annually indefinitely after exposure to the agents listed in Table 2. Results should be reviewed by a physician who is aware that the patient has received cytotoxic therapy.
- At each follow-up, document symptoms (such as fatigue and cutaneous-mucosal bleeding) and conduct physical examinations for clinical signs (such as paleness or hemorrhagic diathesis).
- Bladder cancer: annual evaluation of bladder function in AYACS who were exposed to cyclophosphamide and/or pelvic RT, and who use alcohol and/or tobacco.
- Consider performing a urine sediment test, urine cultures, and calcium/creatinine ratio tests, and refer AYACS with noninfectious hematuria to urologists or nephrologists.
- NHL: Monitor NHL-related symptoms annually, such as swelling, fever, and night sweats.
- Breast cancer: if treated with ≥ 10 Gy chest RT during childhood, surveillance (mammography and breast magnetic resonance imaging [MRI]) is recommended ≥ 8 years from radiation for female AYACS or when reaching 25 years of age (whichever occurs first); thereafter, annual mammography and breast MRI should continue at least up to 60 years of age.
- Monitor AYACS for breast cancer after the following procedures: lymphadenectomy (with or without RT), selective biopsy of the sentinel node, lymph node removal, and high-dose irradiation of the external axillary or inguinal nodes.
- CNS tumors: annual surveillance of symptoms that are progressively worsening (severe, unrelenting headaches, nausea, and vomiting), new-onset (cognitive, motor, sensory, or behavioral changes), or new-onset or worsening balance problems, seizures and other focal neurologic deficits; a brain MRI is recommended only if symptoms appear, except in patients with neurofibromatosis.
- Thyroid cancer: 5 years after RT or radioactive iodine treatment, perform thyroid gland palpation every 1–2 years and/or cervical and thyroid ultrasonography every year for 5 years in AYACS; if nodules are detected, refer the patient to a thyroid specialist.
- Soft tissue sarcomas: frequent self-examination of the skin and soft tissues and annual examination of previously irradiated areas by a physician are recommended [66]. In cases of soft tissue alteration, follow-up with ultrasonography or other imaging tests can be considered.
- Colorectal cancer: perform fecal occult blood tests every 3 years or colonoscopies every 5 years, commencing 5 years after RT or at 30 years of age (whichever occurs last).
- Bone sarcomas: annual consultations to monitor symptoms of bone pain, conduct palpation of bones in radiated fields. X-ray assessment of the bone is recommended in cases of symptoms.

Bone toxicities

A deterioration in bone health (osteoporosis, avascular necrosis, and risk of fractures) can affect up to 20% of AYACS, whose risk of bone fractures can be 4 or 5 times greater than that of the general population of the same age [67–70]. This risk increases when highly aggressive treatments are used more frequently during childhood [71]. The causes of deterioration in bone health are multifactorial and treatment-related and include surgery, immobilization, chemotherapy, RT, corticosteroids, nutritional deficiencies that can affect the metabolism of calcium and vitamin D, hormonal deprivation, and HSCT [4].

If bisphosphonates have been used during therapy, to prevent bisphosphonate-related osteonecrosis of the jaw, a dental examination should be performed regularly, and aggressive dental manipulations should be avoided, especially during the first year after therapy [72].

Recommendations

- The first evaluation in AYA survivors of childhood bone cancer should occur through direct anamnesis, analyses of calcium metabolism, renal function, and hormonal profile.
- Consider the predictive model of bone densitometry to assess the loss of bone mineral density (using factors such as sex, height, weight, attained age, smoking status, and prior exposure to cranial and abdominal irradiation) every year for 2 years after the end of cancer treatment, especially in AYACS who had received RT on the spine or total body [73], and then every 3 years.
- Provide education on preventing fractures and treatments aimed at bone health [74].
- Encourage healthy lifestyle habits, physical exercise, proper nutrition, and calcium and vitamin D supplementation [75].
- Monitor for hormonal alterations or deficits (estrogen and androgen levels).
- If indicated, provide specific treatment for osteoporosis, although there is limited information on the use of bisphosphonates or denosumab in children and adolescents.

Sexuality and fertility

In addition to adolescents facing the challenge of pubertal changes in their bodies and the new sensations associated with sexuality and first intimate contacts, AYACS may be faced with additional difficulties, such as body alterations after surgery, weight gain or loss, stretch marks, scars, and adverse effects (AEs) of cancer treatments [76], which may lead to shame, isolation, loneliness, and immaturity. AYACS who identify as LGBTQ face additional challenges (eg, discrimination and lack of knowledge of specific health needs by clinicians providing oncology care when compared with their non-LGBTQ counterparts [66]).

Impaired fertility in AYACS may result from cancer treatments received during childhood, predominantly alkylating agents, radiotherapy or surgery affecting the gonads [76]. Testicular atrophy and infertility can occur due to lomustine, carmustine, cyclophosphamide, ifosfamide, procarbazine, busulfan, and gonadal radiotherapy treatment in males. Ovarian failure can be caused by tamoxifen, chlorambucil, busulfan, mitomycin, cyclophosphamide, ifosfamide, cisplatin, etoposide, procarbazine, central nervous systems or pelvic irradiation in females [77]. Infertility risk is particularly high in patients receiving conditioning regimens for hematopoietic stem cell transplantation, exceeding 80% in these cases. When faced with long-term consequences that may affect the ability to procreate, options such as fertility-sparing surgery or sperm/egg oocyte or ovarian tissue cryospreservation may need to be considered by AYAs [76], although the success (live births) of these approaches for the female population is ~ 30% [78]. Strategies to protect fertility should be offered before the initiation of treatment for AYAs. In addition, the best approach for preserving future fertility is the use of appropriate chemotherapeutic alternatives with less gonadal toxicity (eg, BRECADD instead of BEACOPP or OEPA instead of COPP in young patients with Hodgkin lymphoma [79]).

Recommendations

- Investigation of the patient´s reproductive goals and expectations, addressing not only biological fertility but also the emotional, sexual and psychological dimensions of reproduction.
- Periodic evaluation of gonadal function, including clinical assessment, hormonal profile (LH, FSH, anti-Müllerian hormone, estradiol/testosterone), spermiogram or antral follicle count.
- Timely referral to fertility specialists for individualized counseling and treatment.

Psychosocial aspects

Adolescence is a period of life marked by physical and mental changes and is influenced by life experiences. It features the development of independence of thoughts and ideals, separation from parents, the development of relationships with peers, an autonomous social life, responsibility for one's body and actions, a sexual identity, couple relationships, the making of decisions in education and work, and the selection of future objectives and goals [80]. However, AYAs who have experienced cancer as children are subject to abrupt cutoffs from their usual lives at the time of diagnosis, prolonged periods of hospitalization, and high long-term dependence on their parents/caregivers. A study in the Netherlands highlighted the consequences of these disruptions caused by cancer, showing that AYA survivors of childhood cancer demonstrated delays in attaining certain milestones in comparison with their peers [81]. Furthermore, while AYACS tend to have better social networks than non-cancer controls, their experienced perception of loneliness (social isolation) is greater [82]. Understanding the possible threat of death posed by cancer causes further anxiety, stress, and depression; a study from the Netherlands reported that 69% of AYA survivors of childhood cancer feared relapse [83]. Numerous psychological and social factors affected by childhood cancer present long-term challenges for AYACS [84].

Education/employment

Cancer diagnoses can interrupt the educational path by precipitating absenteeism, a lack of autonomy, and the feeling of being left behind. Post-treatment difficulties may also be associated with reintroduction into the educational or employment environment [82, 85]. Adaptations to the job/workplace may be necessary to assist AYACS when they return to their places of employment because of the neurocognitive/physical sequelae of the disease, temporary disability, cancer relapses, or stressful situations at work [86].

Family and social relationships

Poor social functioning after a cancer diagnosis can negatively affect a patient's physical and mental outcomes, alter their role in society, and limit the activities they can do that could contribute to a better HRQoL [87]. Childhood cancer can lead to a delay in AYACS gaining independence, pursuing employment/a career, establishing economic independence, finding a life partner, and forming a family [82]. Cancer treatment increases the dependence of AYACS on adults for their daily care, decision-making, and emotional and affective needs [82]. In addition, the overprotective nature of parents/caregivers often compromises patient autonomy and slows down the process of separation of the adolescent from their family [5]. Furthermore, AYACS face difficulties with their body image, self-esteem, self-confidence and maturation, and with discussing cancer with their friends; a lack of support, resources, and social skills may cause them to withdraw from their peers and forgo meaningful shared life experiences [5].

A study at the Gregorio Marañón General University Hospital in Spain exploring family interactions found that parents of AYACS seemed more affected by the cancer experience than AYACS themselves, with parents expressing concerns, fears, and doubts about their children's futures. A total of 73% of parents perceived that they were overprotective and cared more for their children with cancer than for their other children. Most parents (74%) stated that their child's cancer diagnosis had changed their lives, but only 23% believed that the changes in their values and perspectives on life were positive [88].

Health-related quality of life

The HRQoL of AYA survivors of childhood cancer is lower than healthy age- and sex-matched individuals, with the most significant differences observed in cognitive aspects, social functioning, and fatigue [89].

Recommendations

- AYACS should be enrolled in programs to facilitate the prompt resumption of their usual family life, which should include social and educational activities at facilities with age-appropriate areas of care, allowing for privacy, social interaction, and learning and developmental activities.
- The specific psychosocial needs of AYA survivors of childhood cancer should be recognized according to:
    - (i) the type of cancer,
    - (ii) the patient's reaction to the initial cancer diagnosis,
    - (iii) the patients' attitude to treatment (refusal vs. acceptance), as well as to their own mortality,
    - (iv) the type and duration of cancer treatment,
    - (v) the location/visibility of the treatment site on the patient's body,
    - (vi) any existence of a constant reminder of cancer treatment (amputation, surgeries),
    - (vii) the individual's capability for personal growth despite the traumatic cancer experience.
- The importance of educating and training the multidisciplinary team (MDT) on the specific needs of AYACS cannot be overstated.
- Educational support teams should be employed within the educational system to assist AYACS to reach age-appropriate milestones at the same level of learning as their peers and to achieve their highest academic goals.
- Resumption of employment or commencing new employment may present challenges because the work environment may need to be adapted to suit the new physical, neurocognitive, and/or psychosocial needs of AYACS who have undergone treatment for cancer.
- The patient's support network (family, friends, and medical professionals) is recommended to persist in encouraging and supporting AYACS to:
    - (i) play active, fulfilling, ongoing roles in society,
    - (ii) establish and maintain relationships with peers,
    - (iii) participate in social activities frequently to avoid feeling excluded,
    - (iv) practice resilience (ie, balancing stress and coping) and develop goals such as cultivating optimism, finding meaning, connection, and a sense of belonging.
- Provide mental health support for AYACS and their family members from the initial cancer diagnosis until adulthood to ensure that their psychosocial needs are met in the long term, including:
    - (i) counseling of pre-pubertal AYA survivors of childhood cancer on the anticipated changes in physical appearance,
    - (ii) encouraging body positivity,
    - (iii) reinforcing open communication with a trusted confidant in the face of personal challenges, such as exploring sexuality and gender identity and/or fertility concerns.
    - (iv) Clinicians should use subjective but reliable predictors of HRQoL to determine the impact of cancer on the lives of affected AYAs and their families.

Other toxicities

AYACS may develop ototoxicity, either during or in the years after cancer treatment [43], which is usually caused by platinum treatments, including cisplatin, carboplatin, and oxaliplatin, as well as RT to the head region [46, 66]. Hearing impairment may negatively impact HRQoL, school or work performance, and psychosocial functioning in AYACS [43].

Although ocular toxicities are relatively common due to chemotherapy and RT, they often remain underdiagnosed in AYACS. Symptoms such as blurred vision and visual impairment are frequent ocular toxicities due to anticancer therapies [90]. Tamoxifen can increase the risk of corneal deposits, retinopathy, cataracts, and, less frequently, optic neuritis [90]. RT and/or cisplatin can cause the progressive loss of visual acuity and formation of cataracts [91].

Late post-RT-related dermatologic AEs in the treatment field include subcutaneous fibrosis, telangiectasias, hyperpigmentation, alopecia, and nail alteration after chemotherapy [92, 93].

After axillary irradiation, AYAs may experience limited mobility in the ipsilateral scapulohumeral joint. Mobility issues after irradiation of tumors in the scapular region can occur secondary to fibrosis of the pectoral muscle on the affected side or of the subscapularis, infraspinatus, teres minor, and supraspinatus [94–96].

AYACS may also develop pulmonary fibrosis, which can cause respiratory distress, cough, weakness, and weight loss; these symptoms can be prevented with cycles of corticosteroids during the acute phase [97, 98]. Asthenia may persist for years after treatment in 17–30% of AYACS [99, 100]. Chronic cancer pain can result after a mastectomy, chemotherapy for neuropathies, post-RT (mucositis, proctitis, cystitis, enteritis, osteonecrosis, brachial, or lumbosacral plexopathy, neuropathies, etc.), and phantom pain can occur following the amputation of a limb [101].

Recommendations

- Ototoxicity: audiometry should be conducted upon any suspicion of hearing impairment, no later than 1 year after treatment and for 5 years. Patients should be monitored for symptoms such as deafness, earache, and/or tinnitus. Preventing noise pollution is recommended, and ototoxic drugs should be avoided. Further research is required into drugs that reduce ototoxicity (eg, sodium thiosulfate to reduce cisplatin-induced toxicity).
- Skin toxicity: examine AYACS for the following AEs post-radiation every year for at least 2 years:

(i) subcutaneous fibrosis,
(ii) telangiectasias,
(iii) hyperpigmentation,
(iv) lack of recovery from alopecia,
(v) changes in the nails.

- Ocular toxicity: regular eye examinations should be conducted every year for at least 2 years by an ophthalmologist; 5-fluorouracil eye drops can be prescribed to treat dry eye and tear duct fibrosis.

General recommendations

- Collaborate between pediatric and adult services, interdisciplinary care, and early, appropriately timed interventions after diagnosis [102].
- Homogenize the updating of epidemiologic data on AYACS with cancer in Spain by the timely collation of data entered into registries.
- Submit AYACS to a genetic counselling unit in case of familial history and to adjust follow-up to potential hereditary syndromes. Additionally, consider the potential pejorative impact that some follow-up tests, such as CT or X-ray scans, may have in specific hereditary syndromes, like Li-Fraumeni syndrome.
- Ensure open communication and ease of sharing patient information among healthcare providers (eg., primary healthcare facilities should collaborate with the hospital oncologist to ensure continuous care of AYACS) [49].
- Raise suspicion of and actively screen for the most frequently observed cancer types (testicular, Hodgkin lymphoma, leukemia, thyroid, brain and other CNS tumors, NHL, breast, uterine, cervical, and melanoma) in the 15–39 years-old age group [3].
- Involve an MDT consisting of oncologists, pathologists, hematologists, geneticists, surgeons, radiotherapists, psychologists, social workers, physiotherapists, ophthalmologists, otorhinolaryngologists, urologists, nephrologists, dieticians, and AYA-dedicated nurses [75, 103].
- The MDT should receive adequate training on the physical, emotional, psychological, and social needs of AYACS [16, 103] and be involved in initiatives to prevent late toxicities, promote specialized services, and establish specific care models in managing AYACS.
- Clinicians should communicate their expectations to patients accurately and clearly (eg, emphasizing the importance of adherence to treatment and regular follow-up).
- Provide an oncology report at discharge detailing tumor characteristics, treatments received, and requirements for follow-up (with a timeframe for visits, tests, etc.), pain management (if required), and recognizable signs and symptoms of late-onset post-treatment effects that may require immediate medical attention.
- Encourage assimilation back into AYACS' usual lives and maintain a healthy lifestyle:
    (i) regular clinical follow-up,
    (ii) physical exercise,
    (iii) control of lipid intake and maintenance of body weight,
    (iv) alcohol and/or smoking cessation,
    (v) healthy diet (Mediterranean),
    (vi) good-quality sleep.

Table 3 Summary of late-onset toxicities and recommendations in adolescents and young adult cancer survivors

Type of toxicity *Specific risk factors*	Recommendations for patients with mild-moderate risk	Recommendations for patients with high risk*	Interventions
Cardiac *Risk factors*: thoracic RT (high risk if > 35 Gy or in combination with anthracyclines) high dose anthracyclines (> 250 mg/m^2) HSCT	*Follow-up time*: every year. reassess risk at 5 years and individualize follow-up with ECG and echocardiography *Test(s) and frequency*: annual cardiovascular risk assessment, including clinical evaluation, blood pressure measurement, lipid profile, glycated hemoglobin, serum B-type natriuretic peptide (BNP or NT-proBNP)	*Follow-up time*: every year. reassess risk at 5 years and individualize follow-up with ECG and echocardiography *test(s) and frequency*: annual cardiovascular risk assessment, including clinical evaluation, blood pressure measurement, lipid profile, glycated hemoglobin (HbA1c), serum B-type natriuretic peptide (BNP or NT-proBNP). Annual ECG during the first 5 years after cancer treatment, and every 5 years thereafter echocardiography 1, 3, and 5 years after cancer treatment	Strict control of cardiovascular risk factors and structured education on heart-healthy lifestyle habits refer AYACS to a cardiology or cardio-oncology clinic if new cardiovascular signs or symptoms are identified during routine cardiovascular risk assessments by primary care providers
Neurotoxicity and neurocognitive disorders *risk factors*: holocraneal or cranial irradiation intrathecal chemotherapy CNS tumors	*Follow-up time*: 5 years. *Test(s) and frequency*: early neuropsychological evaluation (6 months after treatment) and then every year for 5 years. monitor for ischemic events if cranial RT	*Follow-up time*: 5 years. *Test(s) and frequency*: early neuropsychological evaluation (6 months after treatment) and then every year for 5 years. Monitor for ischemic events if cranial RT	Refer to the neurology department or psychological therapy according to local guidelines in case of alteration
Metabolic syndrome *risk factors*: Previous obesity alkylating agents TKIs HSCT abdominal RT	*Follow-up time*: 10 years *Test(s) and frequency*: healthy living education and counselling BMI control every year Blood test, including glucose, triglycerides, and LDL and HDL cholesterol every 6 months for 2 years. Then, every year for 3 years and afterwards every 2 years for 5 more years follow therapeutic goals for the management of MS refer to endocrinologist in case of diagnosis of MS or DM	*Follow-up time*: at least 15 years (consider unlimited if diagnosis at younger age < 20 yo). *Test(s) and frequency*: healthy living education and counselling. BMI control every year. Blood test, including glucose, triglycerides, and LDL and HDL cholesterol every 6 months for 2 years. Then, every year for 7 more years. Follow therapeutic goals for the management of MS	Refer to endocrinologist in case of diagnosis of MS or DM
Secondary primary malignancies—AML/MDS *risk factors*: Chemotherapy	*Follow-up time*: unlimited *Test(s) and frequency:* clinical exam yearly and blood test	*Follow-up time*: unlimited *test(s) and frequency:* clinical exam yearly and blood test	
Secondary primary malignancies—Breast cancer *risk factors*: RT ≥ 10 Gy to a volume exposing the breasts upper abdominal field radiation that can extend above the diaphragm, likely exposing breast tissue at a young age	*Follow-up time*: 10 years *Test(s) and frequency*: initiate 8 years after RT or at 25 yo, whichever occurs first, with annual exploration and breast MRI/mammography rule out breast cancer hereditary syndrome/familial history	*Follow-up time*: at least 15 years (consider 25 years if diagnosed at younger age) and then include in population screening programs *Test(s) and frequency*: annual exploration and breast MRI/mammography Rule out breast cancer hereditary syndrome/familial history	
Secondary primary malignancies—sarcoma *risk factors*: RT, TBI	*Follow-up time*: 10 years *Test(s) and frequency*: physical examination of irradiated area every year and MRI or ultrasonography if changes in the area	*Follow-up time*: at least 15 years *Test(s) and frequency*: physical examination of irradiated area every year and MRI or ultrasonography if changes in the area	

Table 3 (continued)

Type of toxicity *Specific risk factors*	Recommendations for patients with mild-moderate risk	Recommendations for patients with high risk*	Interventions
Secondary primary malignancies—thyroid cancer *risk factors*: RT to a volume exposing the thyroid gland, including TBI therapeutic^{131} I-MIBG	*Follow-up time*: 10 years *Test(s) and frequency*: initiate 5 years after RT thyroid palpation, T4, and TSH ultrasonography examination every year for 5 years	*Follow-up time*: at least 15 years *Test(s) and frequency*: initiate 5 years after RT Thyroid palpation, T4, and TSH. Ultrasonography examination every year for 5 years	
Secondary primary malignancies—colorectal cancer *risk factors*: RT to a volume exposing the colon and rectum, including TBI	*Follow-up time*: 10 years *Test(s) and frequency*: faecal occult blood testing (preferred) every 3 years or colonoscopy every 5 years, both starting 5 years after radiation or at 30 yo, whichever occurs last rule out colorectal cancer hereditary syndrome	*Follow-up time*: at least 15 years (consider longer follow-up if diagnosis at younger age, < 20 yo) *test(s) and frequency*: fecal occult blood testing (preferred) every 3 years or colonoscopy every 5 years, both starting 5 years after radiation or at 30 yo, whichever occurs last rule out colorectal cancer hereditary syndrome	
Bone toxicities *risk factors*: extended-field RT prolonged corticosteroids exposure Immobilization Hormonal deprivation HSCT	*Follow-up time*: 5 years if no bone density alteration is identified. If osteopenia or osteoporosis, follow-up should be done as in high-risk *Test(s) and frequency*: bone density every year for 2 years and then every 3 years	*Follow-up time*: 10 years *Test(s) and frequency*: bone density every year for 5 years and then every 2 years	If osteopenia or osteoporosis, consider bisphosphonate treatment and refer to a rheumatologist
Sexuality and fertility *risk factors*: any chemotherapy treatment anthracyclines and high-risk alkylating agents oophorectomy/Orchiectomy Pelvic RT	All patients should always be offered a fertility preservation strategy before chemotherapy administration at childhood or young age after treatment: *follow-up time*: depends on the patient's age after 14–15 yo, anamnesis must focus on the regularity of menses or sexual sphere issues at least once. In case of suspicion of infertility or prolonged amenorrhea, refer to a specialist all patients should be offered the possibility of being referred to a specialist at 18 yo		In case of infertility or fertility impairment, refer to a specialist
Ototoxicity *risk factors*: platinum agents cranial irradiation	*Follow-up time*: 5 years *test(s) and frequency*: auditive examination by a specialist no later than 1 year after treatment repeat examination in case of symptoms ask patients about the loss of audition every year	*Follow-up time*: 10 years *Test(s) and frequency*: auditive examination by a specialist no later than 1 year after treatment Repeat examination in case of symptoms. Ask patients about the loss of audition every year	
Skin toxicity *risk factors*: Skin toxicity during treatment	*Follow-up time*: 2 years if complete recovery at least 5 years in case of residual skin toxicity *Test(s) and frequency*: skin examination every year for the first 2 years and then every 2 years	*Follow-up time*: 5–10 years *Test(s) and frequency*: anamnesis and skin exploration (every year for 5 years and then every 2 years)	Refer to a dermatologist if residual skin toxicity

Table 3 (continued)

Type of toxicity *Specific risk factors*	Recommendations for patients with mild-moderate risk	Recommendations for patients with high risk*	Interventions
Ocular toxicity *risk factors*: ADC treatment RT in cranial base previous ocular toxicity during chemotherapy	*Follow-up time*: 2 years if complete recovery at least 5 years in case of residual ocular toxicity *Test(s) and frequency*: ocular toxicity anamnesis and/or exploration every year during the first 2 years and then every 2 years	*Follow-up time*: 5–10 years *Test(s) and frequency*: ocular toxicity anamnesis and/or exploration every year during the first 2 years and then every 2 years	Refer to an ophthalmologist if residual ocular toxicity or symptomatic impairment

ADC, antibody–drug conjugates; BMI, body mass index; CNS, central nervous system; DM, diabetes mellitus; ECG, electrocardiogram; HSCT, hematopoietic stem cell transplantation; MIBG, *meta*-iodobenzylguanidine; MRI, magnetic resonance imaging; MS, metabolic syndrome; RT, radiotherapy; TBI, total body irradiation; TKI, tyrosine kinase inhibitor; TSH, thyroid-stimulating hormone; yo, years old

*General risk factors include treatment with alkylating agents, anthracyclines, or anti-HER2 therapy

- Advise undertaking frequent self-examination and recognizing late-onset post-treatment effects that may require immediate medical attention.
- Invest and research further the management of cancer survivors in the 15–39 years-old group to improve patient outcomes and HRQoL.
- A summary of our recommendations for managing AYACS' potential toxicities is presented in Table 3.

Concluding remarks

Representative experts from six Spanish Societies (SEOR, SEHOP, SEOM, SEMERGEN, SEMG, and SEHH) have provided recommendations to manage late toxicities in AYACS. Compared with the pediatric and adult age groups, AYACS have unique requirements that healthcare professionals often overlook. An MDT should ensure collaboration between primary care facilities and hospitals and provide early neuropsychological examination, continuous mental health support, health education after treatment, and long-term monitoring to prevent or reduce the risk of developing secondary tumors. Patients should be provided with a complete oncology report at discharge detailing the tumor characteristics, treatments received, requirements for follow-up (with a timeframe for visits, tests, etc.), signs and symptoms to recognize for immediate referral, the importance of maintaining a healthy diet, avoiding toxic habits (alcohol, tobacco), regular BP checks and physical exercise, control of lipid intake and body weight, and resources to improve their personal growth and HRQoL. Future research into minimizing the toxicities in the 15–39 age group resulting from childhood cancer treatment is recommended.

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