

NCCN

Adolescent and Young Adult Oncology, Version 2.2018

Clinical Practice Guidelines in Oncology

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Abstract

This selection from the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology focuses on treatment and management considerations for AYA patients with cancer. Compared with older adults with cancer, AYA patients have unique needs regarding treatment, fertility counseling, psychosocial and behavioral issues, and supportive care services. The complete version of the NCCN Guidelines for AYA Oncology addresses additional aspects of caring for AYA patients, including risk factors, screening, diagnosis, and survivorship.

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Overview

Over the past 20 years, advances in cancer treatment have significantly improved survival rates for young children and older adults, but these improvements have generally not applied to adolescent and young adult (AYA) patients.^{1,2} One of the main reasons for the lack of improvement in outcomes is that AYA patients have a low rate of participation in clinical

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At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Adolescent and Young Adult Oncology Panel members can be found on page 97. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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trials.^{1,3-6} In the United States, approximately 10% of patients 15 to 19 years of age and 1% to 2% of patients 20 to 39 years of age are enrolled in clinical trials.⁷ In addition to the low rate of participation in clinical trials, several other factors contribute to the poor outcome in AYA patients, such as differences in disease biology, lack of consistency in treatment approaches, poor adherence or intolerance to therapy, lack of health insurance, delays in diagnosis, and physician's lack of familiarity with cancer in the AYA population.⁸ AYA patients also face unique developmental and psychosocial issues that make adjustment to their disease, health-maintenance, and financial hardships more challenging.^{6,9-12}

The biology, epidemiology, and clinical outcomes affecting AYA patients are usually different than those of younger and older patients with cancer.^{13,14} In addition, the genetic, physiologic, and pharmacologic changes as-

sociated with AYA patients may impact their ability to tolerate cancer therapy and their response to treatment. Moreover, short- and long-term toxicities impacting a young, independent patient—including the impact of treatment on fertility—may disincentivize treatment, leading to gaps in adherence and poor outcomes. Attention to these issues and providing options that empower the patient at the time of initial cancer treatment may result in more successful implementation of the planned therapy. Unlike comprehensive geriatric assessment, which is helpful to physicians in developing a coordinated treatment plan and understanding the functional needs of older patients, no similar assessment has been reported for AYA patients. There are less evidence-based data to guide the treatment of AYA patients. AYA

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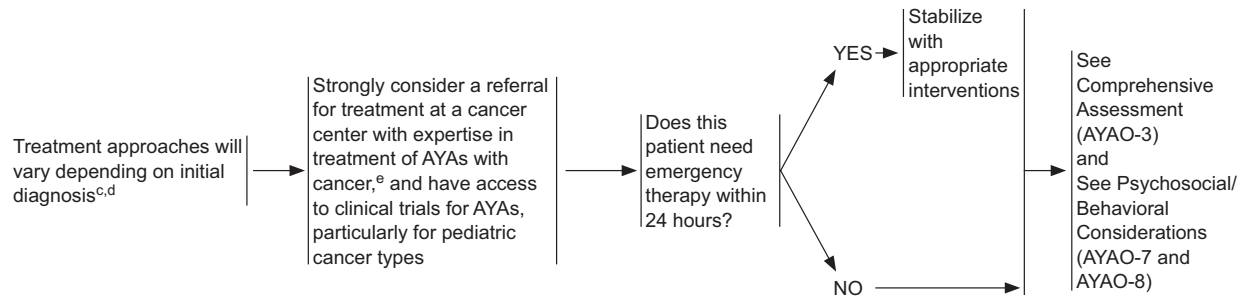
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SCREENING, ASSESSMENT, AND EVALUATION



*Available online, in these guidelines, at NCCN.org.

^cSee Age-Specific SEER Incidences of Cancer by Age Group and Sex in the AYA Population (2008–2012) (AYAO-4*).

^dSee Definition of AYA Population (AYAO-1*).

^eThese centers provide a multidisciplinary approach involving a team of providers with expertise in cancer treatment and management of specific mental health and developmental issues such as fertility, education, career development, employment, family planning, pregnancy, sexually transmitted diseases, smoking, and substance abuse.

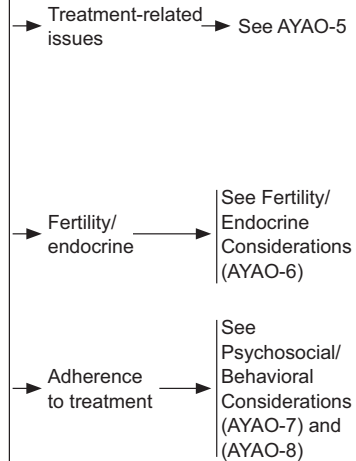
AYAO-2

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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COMPREHENSIVE ASSESSMENT

- Provide age-appropriate information related to cancer
See Online Resources for AYA Patients and Survivors (AYAO-D*)
- All women of child-bearing potential must receive a pregnancy test prior to initiating therapy
- Discuss contraception prior to initiating therapy
- Discuss risks of infertility due to cancer and its therapy, as well as options for fertility preservation
See Fertility/Endocrine Considerations (AYAO-6)
- Psychosocial assessment
 - ▶ See Psychosocial/Behavioral Considerations
 - ◊ Individual (AYAO-7 and AYAO-8)
 - ◊ Relationships (AYAO-9)
 - ◊ Socioeconomic Issues (AYAO-10)
 - ▶ See NCCN Guidelines for Distress Management†
- Recommend referral for genetic and familial risk assessment/counseling as appropriate based on clinical/family history and histologic diagnosis
 - ▶ Risk factors for breast cancer
 - ◊ Germline mutations of *BRCA1*, *BRCA2*, *TP53* (Li-Fraumeni syndrome), or *PTEN* (Cowden syndrome)
See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian†
 - ◊ Chest irradiation
 - ▶ Risk factors for colon cancer
 - ◊ Mutations in *MMR* genes [hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome)] or *APC* genes [familial adenomatous polyposis (FAP)]
See NCCN Guidelines for Colorectal Cancer Screening†
 - ▶ Risk factors for sarcomas See NCCN Guidelines for Soft Tissue Sarcoma†
 - ◊ Li-Fraumeni syndrome
 - ◊ Germline mutations in the retinoblastoma (*Rb*) gene or succinate dehydrogenase (*SDH*) gene. Testing for germline mutations in the *SDH* subunit genes should be considered for AYAs with wild-type gastrointestinal stromal tumors (GIST) (lacking *KIT* or *PDGFRA* mutations) or paragangliomas
 - ◊ FAP-associated desmoid tumors (aggressive fibromatosis) See NCCN Guidelines for Colorectal Cancer Screening†
 - ◊ Germline mutations in neurofibromatosis-1 (*NF-1*) gene are associated with malignant peripheral nerve sheath tumor (MPNST)
 - ▶ Risk Factors for Multiple Endocrine Neoplasms (MEN)
 - ◊ See NCCN Guidelines for Neuroendocrine Tumors†



*Available online, in these guidelines, at NCCN.org.

†Available at NCCN.org.

AYAO-3

TREATMENT-RELATED ISSUES

Dose schedules



- Selected AYA patients may tolerate more intensive therapies than older patients
 - ▶ Dose intensity and dose density are associated with improved outcomes^h
 - ▶ See NCCN Guidelines for Myeloid Growth Factors[†] for growth factor support
- Dose reductions are often based upon avoiding severe, irreversible organ damage
 - ▶ Assume that the patient population has a significant long-term survival and that significant end-organ damage may compromise long-term function and quality of life
- Monitoring of cumulative dosing and schedule for certain medications associated with irreversible organ damage and fertility issues may be essential when certain lifetime exposure is encountered. See AYAO-11* for specific agents
- Maximum cumulative dosing parameters are often established for a patient to reduce the risk of significant irreversible damage

Toxicities



- Reversible toxicities do not necessarily warrant dose reductions. See NCCN Guidelines for Supportive Care[†] for the management of treatment-related toxicities, including:
 - ▶ See NCCN Guidelines for Adult Cancer Pain[†]
 - ▶ See NCCN Guidelines for Antiemesis[†]
 - ▶ See NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia[†]
 - ▶ See NCCN Guidelines for Cancer-Related Fatigue[†]
 - ▶ See NCCN Guidelines for Palliative Care[†]
 - ▶ See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections[†]
- Screening is recommended for the following treatment-related toxicities:
 - ▶ Cardiac toxicity - Regular echocardiograms. A baseline electrocardiogram (ECG) is only recommended after completion of treatment - See Screening Recommendations (AYAO-B*). Recommend adding cardioprotectant (eg, dexrazoxane) for patients receiving an anthracycline.
 - ▶ Renal toxicity - Regular glomerular filtration rate (GFR) calculations to monitor renal toxicity associated with cisplatin- and ifosfamide-based chemotherapy
 - ▶ Neurotoxicity - Regular audiogram to monitor hearing loss associated with cisplatin- or carboplatin-based chemotherapy
 - ▶ Routine endocrine, ophthalmology, and dental evaluations for patients with selected radiation exposure and/or total body irradiation (TBI) for stem cell transplant
 - ▶ Infertility - See Screening Recommendations (AYAO-B, 3 of 3*)

*Available online, in these guidelines, at NCCN.org.

†Available at NCCN.org.

^hWomer RB, West DC, Krailo MD, et al. J Clin Oncol 2012;30:4148-4154. DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Leukemia 2015;29:526-534. Gerber NK, Wexler LH, Singer S, et al. Int J Radiat Oncol Biol Phys 2013;86:58-63.

AYAO-5

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FERTILITY/ENDOCRINE CONSIDERATIONS

- Fertility preservation as well as sexual health and function should be an essential part in the management of AYAs with cancer who are at any risk for infertility due to cancer treatmentsⁱ
- Discuss risks for infertility due to cancer and its therapy (especially for high-risk therapies such as alkylating agents or gonadal irradiation), fertility preservation, and contraception prior to the start of therapy^j
 - ▶ Men are at risk for azoospermia following therapy, which may or may not resolve over time
 - ▶ Women are at risk for premature ovarian failure following therapy

- Initiate referral for fertility preservation clinics within 24 hours for all patients who choose the option of fertility preservation
- Refer to a mental health professional to assist with complex decision making if needed. See Psychosocial/Behavioral Considerations (AYAO-7 and AYAO-8)

Males

- Discuss the option of sperm banking
- Suggest a local sperm bank, or available online sperm banking kit
- Consider follow-up with fertility specialist post-treatment

Females

- Discuss the option of embryo or oocyte cryopreservation or ovarian tissue cryopreservation (if available)
 - ▶ Initiate if provider deems that therapy can be delayed long enough for a cycle of oocyte stimulation (for low- and intermediate-risk Hodgkin's lymphoma, low-grade sarcomas, and breast cancer)
- Consider follow-up with fertility specialist post-treatment
- Oophoropexy
 - ▶ Ovaries may be surgically moved away from the planned radiation field, either during cancer surgery or in a separate procedure
- Menstrual suppression
 - ▶ Medroxyprogesterone, oral contraceptives, or gonadotropin-releasing hormone (GnRH) agonists may be used in protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia
 - ▶ It is controversial whether menstrual suppression would protect the ovaries, but some data suggest that menstrual suppression with GnRH agonists may protect ovaries in young women with breast cancer before the initiation of chemotherapy^k

ⁱLevine J, Canada A, Stern CJ. Fertility preservation in adolescents and young adults with cancer. *J Clin Oncol* 2010;28:4831-4841.

^jThe impact of cancer therapy on fertility is related to the age of the patient at the time of treatment and is dependent on the duration, dose intensity, and type of treatment. See NCCN Guidelines for Breast Cancer for the management of women with breast cancer during pregnancy (available at NCCN.org).

^kMoore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med* 2015;372:923-932.
Demeestere I, Brice P, Peccatori FA, et al. No evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial. *J Clin Oncol* 2016;34:2568-2574.

AYAO-6

PSYCHOSOCIAL CONSIDERATIONS: INDIVIDUAL EVALUATION

- Psychosocial factors:
 - ▶ Cognitive function
 - ◊ Developmental stage
 - ▶ Communication preferences and potential barriers (eg, literacy and language considerations as well as preferred learning methods)
 - ▶ Adjustment to illness
 - ◊ Provide opportunity for patient to share his/her cancer story.
 - ▶ (See NCCN Guidelines for Distress Management†)
 - ▶ Evaluate for current and past psychiatric symptoms, including anxiety and depression
 - ▶ Involvement/interruption of school/work
 - ▶ Living status
 - ◊ Alone
 - ◊ Spouse/partner
 - ◊ Parents
 - ◊ Children
 - ▶ Impact of cancer on identity
 - ◊ Personal values
 - ◊ Self-esteem
 - ◊ Relational identity
 - ◊ Body image and physical changes
 - ◊ Strengths/resilience
 - ◊ Future goals

SUPPORTIVE CARE SERVICES/INTERVENTIONS

- Refer AYA patients with cognitive dysfunction or other psychiatric symptoms (eg, depression, anxiety) to a mental health provider and community-based resources serving AYA patients
- Offer psychosocial support and counseling to help alleviate distress (See NCCN Guidelines for Distress Management†).
- Consider flexible treatment dates, consultation times, and procedures (evenings/weekends)
- For all AYA patients, provide counseling around decision-making regarding the risks of treatment-related infertility and discuss options for fertility preservation prior to the start of therapy. See Fertility/Endocrine Considerations (AYAO-6)

Individual: Behavioral factors → See AYAO-8

Relationships → See AYAO-9

Socioeconomic issues → See AYAO-10

†Available at NCCN.org.

AYAO-7

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BEHAVIORAL CONSIDERATIONS: INDIVIDUAL EVALUATION

- Behavioral factors:
 - ▶ Adherence to therapy
 - ▶ Tobacco, alcohol, cannabis, or other substance use/abuse
 - ▶ Sexual behavior/risks/concerns
 - ▶ Assess nutritional requirements and potential deficits based on age
 - ▶ Exercise needs, hobbies, and recreational activities
 - ▶ Sleep patterns
- Use of both integrative therapies and complementary and alternative medicine (CAM)
- Existential/spiritual issues

SUPPORTIVE CARE SERVICES/INTERVENTIONS

- Adherence to therapy
 - ▶ Educate about the expectations of treatment and explain the patient's responsibility to adhere to therapy
 - ▶ Provide education and/or guidance about each medication prior to the start of treatment and every time there is a change in treatment.
 - ▶ Review list of medications and their dose, purpose, and adverse effects. Simplify dosing schedule and change timing and frequency of medication or method of administration, when medically possible, to fit into AYAs' lifestyle and normal activities
 - ▶ Provide access to systematic and standardized symptom management for side effects related to cancer treatment. See NCCN Guidelines for Supportive Care†
- Refer to smoking cessation program if needed. See NCCN Guidelines for Smoking Cessation†
- Provide education about the impact of early cannabis use on cognitive development and mental health
 - ▶ If AYA chooses to continue use, provide education on risks and benefits of varying methods of ingestion and dosing
- Refer patients with signs, symptoms, and a history of substance abuse or addiction to a risk reduction or substance abuse management program
- Provide education about the impact of treatment on sexual health including safe sexual practices in light of risk of infection, risk for bleeding, prevention of pregnancy, and sexually transmitted diseases. See WHO recommendations in the Discussion section
- Provide education about potential diet/nutritional changes associated with cancer treatment and possible interventions. Refer to registered dietitian-certified specialist in oncology (RD-CSO)
- Refer to reputable providers of integrative therapies and CAM services.
- Refer patients experiencing challenges with their faith or belief in a just or fair world to faith-based resources or activities (eg, church youth groups, mentors). If necessary, refer to a chaplain or pastoral counselor

Relationships —————▶ See AYAO-9

Socioeconomic issues —————▶ See AYAO-10

†Available at NCCN.org.

AYAO-8

PSYCHOSOCIAL/BEHAVIORAL CONSIDERATIONS: RELATIONSHIPS
EVALUATION

- Family status
 - ▶ Interaction and relationship with parents
 - ▶ Interaction and relationship with spouse/partner
 - ▶ Interaction and relationship with sibling(s)
 - ▶ Patient with young children
- Peer relationships
- Sexual orientation
- Participation in community and social activities (eg, religious organizations, clubs, athletics/recreation, music, youth groups)
- Communications with health care professionals
 - ▶ Decision-making preferences: family, friend, clinical care team, and/or self
 - ▶ Information and communication preferences (eg, visual, auditory)
 - ▶ Consider role of cultural and/or family values



SUPPORTIVE CARE SERVICES/INTERVENTIONS

- Promote communication between AYA patients and family members:
 - ▶ Parents
 - ▶ Spouse/partners
 - ▶ Siblings
- Provide family members and partners with information about psychosocial support and behavioral services.
 - ▶ Increase awareness of the possible psychosocial issues associated with cancer diagnosis in AYAs, so that family members and partners may continue to support the patient.
- Consider the following family-based intervention models from pediatric studies, which may have utility for AYAs:
 - ▶ Parent support groups
 - ▶ AYA support groups
 - ▶ Social and recreational programs
 - ▶ Psychoeducational programs
- Provide information about peer support to assist AYAs establishing and maintaining relationships with their peers as well as with other AYAs with cancer. See Online Resources for AYA Patients and Survivors (AYAO-D*)
 - ▶ Face-to-face meetings
 - ▶ Camp and retreat programs
 - ▶ Online support groups
 - ▶ Social networking opportunities
- Create flexible visiting hours and an environment that will encourage peers to visit AYA patients.
- Communicate directly with individual patients.
 - ▶ Ask for permission to share information with family members.
 - ▶ Provide developmentally appropriate information about their cancer, treatment options, and potential side effects. See Online Resources for AYA Patients and Survivors (AYAO-D*)
- Encourage completion of a medical power of attorney when appropriate.

*Available online, in these guidelines, at NCCN.org.

AYAO-9

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PSYCHOSOCIAL/BEHAVIORAL CONSIDERATIONS: SOCIOECONOMIC ISSUES

EVALUATION

- Insurance availability and security
 - ▶ Employer-provided
 - ▶ Parent's insurance
 - ▶ Health insurance marketplace
- Assessment of risk for losing insurance
 - ▶ Loss of employment
 - ▶ Age out of parents' insurance
- Risk for financial loss or bankruptcy
- Child care
- Transportation
- Accommodation if traveling to receive treatment
- Stability of housing and basic household socioeconomic needs

SUPPORTIVE CARE SERVICES/INTERVENTIONS

- Link qualified AYA patients to Medicaid, social security, and/or disability insurance
- Educate AYA patients about benefits they may qualify for, such as short- or long-term disability, state disability benefits, and public assistance
- Provide information on obtaining financial assistance with fertility needs. Local and institutional grants may be available
- Refer for career counseling and/or education support as indicated.
- Direct AYA patients to legal resources/advocates for understanding health insurance coverage
- Identify resources for respite care for AYA patients with young children.
- Refer to transportation assistance programs (eg, van ride programs, voucher programs)
- Provide AYAs with a list of recommended and reliable online sources to access information related to their cancer. See Online Resources for AYA Patients and Survivors (AYAO-D*)
- Financial assistance for AYA cancer survivors needs to be integrated into survivorship plans.
- AYAs with cancer need long-term follow-up care for monitoring and treatment of late effects long after completion of treatment

*Available online, in these guidelines, at NCCN.org.

AYAO-10

PALLIATIVE CARE and END-OF-LIFE CONSIDERATIONS

Palliative care focuses on symptom control, reduction of physical suffering or discomfort, and optimizing quality of life at any stage of a life-threatening disease (see NCCN Guidelines for Palliative Care, available at NCCN.org). Referral to palliative care is appropriate when patients are being treated with curative intent and can be initiated at the time of initial diagnosis.¹ A palliative care team is multidisciplinary, with resources and expertise to address the psychosocial, emotional, and physical challenges relevant to the patient.² Strategies to support a patient, particularly in the AYA population, must be individualized in context of the family dynamic, including maturity of the patient and level of independence (both desired and actual).

End-of-life considerations

- Palliation of symptoms is an important aspect of end-of-life care.
- It is imperative for health care professionals not to assume that AYA patients may be less inclined to discuss death and other end-of-life issues.²
- Discussion about end-of-life preferences should begin early in treatment, but details should be individualized according to the preferences of the AYA patient and family.³
- Many adolescents indicate a preference for dying at home, yet 80% die in hospitals.^{4,5}
- Physicians with experience in end-of-life care should facilitate discussion about issues such as nutrition/hydration, sedation treatment cessation, and place of death.²
- An advance care planning document is recommended for terminally ill AYA patients with metastatic cancer.^{3,6}
- Ongoing psychosocial support is extremely important during the transition to end-of-life care. For family and friends, grief from loss may begin before death.

¹Pritchard S, Cuvelier G, Harlos M, Barr R. Palliative care in adolescents and young adults with cancer. *Cancer* 2011;117:2323-2328.

²Wein S, Pery S, Zer A. Role of palliative care in adolescent and young adult oncology. *J Clin Oncol* 2010;28:4819-4824.

³Wiener L, Zadeh S, Wexler LH, Pao M. When silence is not golden: Engaging adolescents and young adults in discussions around end-of-life care choices. *Pediatric Blood & Cancer* 2013;60:715-718.

⁴Bell CJ, Skiles J, Pradhan K, Champion VL. End-of-life experiences in adolescents dying with cancer. *Support Care Cancer* 2010;18:827-835.

⁵Webb NM, Tucker D. Young adults' opinions about hospice and home death. *J Palliat Med* 2009;12:337-342.

⁶Wiener L, Ballard E, Brennan T, et al. How I wish to be remembered: the use of an advance care planning document in adolescent and young adult populations. *J Palliat Med* 2008;11:1309-1313.

AYA0-C

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Cont. from page 67.

patients diagnosed with cancer should be recognized as a distinct age group that has unique medical and psychosocial needs.¹⁵ The distinct biology of disease and age-related issues in AYA patients should be considered in the treatment decision-making process.¹⁶

The AYA patient is generally defined as an individual 15 to 39 years of age at the time of initial cancer diagnosis.^{6,17} Nearly 70,000 people in this age group are diagnosed with cancer each year in the United States, which is more than 7 times more people than are diagnosed at younger than 15 years of age.¹⁷ Compared with children younger than 15 years, 5-year relative survival in AYA patients is worse for those with acute lymphoblastic leukemia, acute myeloid leukemia (AML), Hodgkin lymphoma (HL), non-Hodgkin's lymphoma (NHL), astrocytomas, Ewing sarcoma, rhabdomyosarcoma, or osteosarcoma.¹⁸ Additionally, for Ewing sarcoma, outcomes are worse for patients ≥ 18 years of age compared with patients < 18 years.^{19–21} Conversely, 5-year relative survival is better in AYA patients with medulloblastomas and germ-cell tumors compared with in children with these tumors, possibly reflecting biologic differences in the tumors of each age group. Compared with adults 40 years and older, AYA patients tend to have better survival rates, except for those with breast and prostate cancer.¹⁸ Increasing age is associated with poorer prognosis in AYA patients with AML, NHL, Burkitt and Burkitt-like lymphoma, or rhabdomyosarcoma.²² Female AYA patients tend to have better 5-year relative survival compared with male AYA patients.¹⁸

The spectrum of cancer types that affect the AYA population is unique and different from the types that affect the pediatric and older population. Cancer is the leading cause of death among the AYA population, excluding homicide, suicide, or unintentional injury.^{8,23} Lymphomas, melanoma, testicular cancer, female genital tract malignancies, thyroid cancer, bone and soft tissue sarcomas, leukemias, central nervous system (CNS) cancers, breast cancer, and non-gonadal germ cell tumors account for 95% of the cancers in this age group.^{1,24} The frequency and incidence of distribution of cancer types is also dramatically different across the age spectrum of AYA patients (see Table 1).

Quality care for AYA patients with cancer is tied to timely detection and start of treatment, adherence to treatment, and access to a multidisciplinary

Table 1. Age-Specific SEER Incidences^a of Cancer by Cancer Site and Sex in the AYA Population (2010–2014)

Women		Men	
Cancer Type	Ages 15–39 y	Cancer Type	Ages 15–39 y
Carcinoma of breast	21.0	Germ cell neoplasms	11.2
Thyroid carcinoma	18.3	Melanoma	5.0
Carcinoma of cervix and uterus	8.9	NHL	4.7
Melanoma	8.5	Carcinoma of colon and rectum	4.2
Carcinoma of colon and rectum	4.0	Leukemias	3.9
HL	3.4	Thyroid carcinoma	3.9
NHL	3.2	HL	3.5
Leukemias	2.9	Soft tissue sarcomas	3.2
CNS cancers	2.5	CNS cancers	3.3
Soft tissue sarcomas	2.3	Carcinoma of the kidney	2.4
Carcinoma of the kidney	1.7	Carcinoma of head and neck	1.7
Carcinoma of head and neck	1.4	Bone sarcomas	1.1
Germ cell neoplasms	1.0		

Abbreviations: CNS, central nervous system; HL, Hodgkin lymphoma; NHL, non-Hodgkin's lymphoma.

^aIncidence rates per 100,000.

Data from Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975–2014, National Cancer Institute. Bethesda, MD. Available at: https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER website, April 2017.

team of healthcare professionals who are well-versed in the specific developmental issues relevant to this patient population.^{25,26} These issues include fertility, long-term side effects, psychosocial and socioeconomic issues, transportation to clinic appointments, maintaining school and work obligations, child care, treatment adherence, and the unique biology of disease. The relative importance of these issues varies considerably across the broad age range defined as AYA. Certain institutions have established centers specialized in accommodating the specific needs of AYA patients. A retrospective population-based analysis in California found that although the percentage of AYA patients who received care from a specialized cancer center increased over the past 20 years (27% in 1991 to 43% in 2014), a minority of AYA patients receive care at specialized cancer centers.²⁷ Referral of patients to AYA centers of excellence should be considered if feasible.

The goals of the NCCN Guidelines for Adolescent and Young Adult Oncology are to identify issues specific to AYA patients and recommend interventions unique to these patients; educate physicians regarding the prevalence of cancer in the AYA population and its long-term consequences; and identify special considerations related to the management of cancer in AYA patients with the aim of improving treatment tolerance, adherence, and clinical outcomes; and to promote participation in clinical trials and enrollment on tumor banking and biologic protocols.

Management of AYA Patients With Cancer: Special Considerations

AYA patients should be managed by a multidisciplinary team of providers with expertise in cancer treatment and management of specific developmental issues such as fertility, education, career development, employment, family planning, pregnancy, sexually transmitted diseases, and tobacco, alcohol, and substance abuse. Given the rarity of several tumor types diagnosed in this population, all AYA patients should be offered and encouraged to participate in tumor banking studies and multicenter clinical trials, when available.

All AYA patients should undergo comprehensive assessment after the diagnosis of cancer, which should include psychosocial assessment, discussion of risks of infertility associated with cancer and its treatment, the use of and education concerning fertility preservation and contraception, and genetic and familial risk assessment as appropriate based on clinical history, family history, and/or histologic diagnosis. Age- and developmentally-appropriate information related to cancer should be provided and women of childbearing potential must receive a pregnancy test before the start of therapy.

Age-Appropriate Care

AYA patients can be treated either at pediatric or at adult cancer centers.²⁵ Retrospective analyses have shown that AYA patients with certain pediatric-type cancers, such as ALL,^{22,28-31} rhabdomyosarcoma,³² and Ewing sarcoma,³³ have superior outcomes when treated with pediatric protocols. Alternatively, there is a lack of compelling evidence that pediatric proto-

cols improve outcomes in AYA patients with AML, HL, and NHL.³⁴⁻³⁶

As mentioned earlier, the low rate of participation in clinical trials is one of the main reasons for the lack of improvement in outcomes in AYA patients with cancer.^{1,3,4,22} A review of 30 studies of adolescents with cancer (ages 15–19) showed that 5% to 34% of these patients enrolled in clinical trials.²² In 20 to 25 year olds, clinical trial enrollment further decreases to approximately 2%.³⁷ Care should be provided at medical centers with broad access to clinical trials (standard-of-care registry trials and trials evaluating novel therapies).²⁵ Pediatric cancer centers enroll more adolescents into clinical trials (35% vs 12% at non-pediatric cancer centers), and AYA patients treated at pediatric cancer centers have a higher rate of clinical trial enrollment (26%) compared with those treated at adult cancer centers (4%).³⁸⁻⁴⁰ Parsons et al⁴¹ reported that AYA patients who are treated by non-pediatric oncologists are less likely to be enrolled in clinical trials. Nevertheless, a substantial number of AYA patients with pediatric malignancies are not being treated at pediatric cancer centers.^{22,42,43}

The treatment and appropriate location of care vary with the type of cancer as well as with the availability of family, community, and institutional support.^{8,44} Most importantly, AYA patients should be evaluated at medical centers with extensive experience in treating cancer in this patient population and at centers that have access to supportive care services (psychosocial/educational support and fertility preservation) specific to the AYA population as well as to medical subspecialty services appropriate to the cancer diagnosis, such as orthopedic surgeons with experience in limb-sparing surgery for patients with extremity sarcomas.²⁵ In a supportive care needs survey that assessed the information and service needs of young adults with cancer at a single institution, most young adults with cancer identified the following information as most important: information on their specific malignancy, effects of treatment on fertility, information on maintaining a healthy diet, and exercise/physical fitness during cancer treatment.⁴⁵ Cancer centers should adopt the appropriate evidence-based approach, which includes adult centers implementing treatment based on pediatric protocols that have demonstrated superior outcomes in AYA patients and pediatric centers adopting adult

regimens that have demonstrated benefit in this patient population.

Treatment Options

Selected AYA patients may tolerate more intensive therapies than older patients, since they have fewer comorbid conditions that limit the intensity of treatment in some older adults.⁸ Dose-intensive and dose-dense treatment is associated with improved outcomes in some malignancies.^{19,46,47} Therefore, more intensive therapy may be considered for every AYA patient if such a regimen exists for that particular disease and there are no contraindications.

Treatment-related issues in AYA patients may differ from those of pediatric or older adult patients due to the distinct biology of the disease.¹³ Physical and physiologic changes, such as changes in body composition, size and maturity of organs, and hormones associated with the normal pubertal process, may directly affect the drug disposition, drug efficacy, and toxicity of chemotherapy in AYA patients.⁴⁸ Appropriate management of symptoms and side effects to reduce the severity and toxicity of treatment should be an integral part of the management of AYA patients.⁴⁹ Surgery, radiation therapy (RT), chemotherapy, and hematopoietic stem cell transplant (HSCT) are the main treatment options for patients who are able to tolerate curative treatment. All of these options are associated with both acute and late side effects.^{8,50}

Surgery: Surgery plays an important role in the management of cancer in AYA patients, especially in breast and thyroid cancer, melanoma, bone, and soft-tissue sarcomas that are more common in AYA patients. Adolescent patients, whose bodies are still developing, may be more affected by some surgical procedures than older patients who are already at or near their full body size.⁸ The extent of surgery is dependent on the type and location of cancer. In some cases, extensive surgery requiring removing part or all of an organ or limb may be necessary. With advances in surgical techniques and chemotherapy, limb-sparing surgery is feasible for most patients with extremity sarcoma and osteosarcoma.⁴⁹ It is imperative that surgery should be performed in high-volume centers by surgeons with expertise in the management of AYA patients, with access to rehabilitative services to ensure that function is preserved as much as possible.

RT: RT is associated with an increased risk for late mortality; development of second malignancies; pulmonary, cardiac, and thyroid dysfunction; and chronic health conditions and growth abnormalities.⁵¹ AYA patients receiving RT to testes or ovaries are at risk of developing infertility later in life.⁵² Women with HL who receive chest RT between 10 and 30 years of age are at increased risk of developing breast cancer.⁵³ Cranial RT is associated with short stature, cognitive processing difficulties, and poor physical function, which contribute to lower rates of employment, independent living, and marriage among AYA cancer survivors.⁵⁴ Adolescents are more vulnerable to RT-induced spinal cord dysfunction, presumably because of elongation of the cord during the growth spurt.⁵⁵

Chemotherapy: Pain, fatigue, nausea, vomiting, mucositis, hair loss, infection, and myelosuppression are some of the acute side effects of chemotherapy. Reversible toxicities do not necessarily warrant dose reductions. See the NCCN Guidelines for Supportive Care (available at www.NCCN.org) for the management of treatment-related toxicities. Every attempt should be made to maintain dose intensity unless it is contraindicated. Dose reductions are often based on avoiding severe, irreversible organ damage. Significant end-organ damage may compromise long-term function and quality of life in AYA patients. Maximum cumulative dosing parameters are often established for a patient to reduce the risk of significant irreversible damage. Monitoring of cumulative dosing and dose schedule along with intensive screening is essential for patients receiving chemotherapy regimens associated with irreversible organ damage and/or infertility.

Anticipatory nausea and vomiting (ANV), also known as conditioned, learned, or psychological nausea and vomiting, is reported to occur before chemotherapy in approximately 20% of patients at any one chemotherapy cycle and in 25% to 30% of patients by their fourth chemotherapy cycle.⁵⁶ Younger patients (younger than 50 years of age) may be more susceptible to ANV, because they generally receive more aggressive chemotherapy and have poorer emesis control than older patients.⁵⁶ Behavioral therapy has been used in patients with ANV⁵⁷ (see the NCCN Guidelines for Antiemesis).

Alkylating agent-based chemotherapy is associated with a higher risk of infertility in both male

and female patients⁵² (See “Impact of Cancer and Its Treatment on Fertility,” page 81). Anthracycline-based chemotherapy is associated with cardiac dysfunction, whereas neurotoxic chemotherapies such as methotrexate and cytarabine can result in CNS dysfunction.⁴⁹ Bleomycin-induced pulmonary toxicity is well documented in patients with HL treated with bleomycin-containing chemotherapy regimens.⁵⁸ Higher cumulative doses of cisplatin, ifosfamide, or epipodophyllotoxins are associated with hearing loss, renal dysfunction, and secondary AML, respectively.^{59–62} See also the section on “Late Effects in AYA Cancer Survivors” in the complete version of these guidelines (available at NCCN.org).

HSCT: HSCT is a potentially curative treatment option for an increasing number of AYA patients with leukemias and lymphomas.⁶³ Graft-versus-host disease (GVHD), chronic immunosuppression, and gonadal dysfunction in males and females related to high-dose conditioning chemotherapy and RT are the major post-transplant complications associated with HSCT.^{49,50}

Chronic GVHD has been identified as the leading cause of non-relapse mortality in HSCT survivors.⁶⁴ AYA patients are at a higher risk of developing chronic GVHD than younger children.⁶⁵ Patient age older than 15 years (children younger than 5 years had a probability of less than 14% compared to a probability of 44% for patients older than 15 years) and the use of total body irradiation (TBI) were significantly associated with an increased likelihood of developing chronic GVHD after allogeneic HSCT.⁶⁶ Patients receiving peripheral stem cells during their transplant procedure have a greater risk of chronic GVHD compared with those who received bone marrow transplant.⁶⁷ A report from the Bone Marrow Transplant Registry demonstrated that chronic GVHD had a significant impact on the overall health status of HSCT survivors, particularly in the areas of functional impairment, activity limitation, and pain.⁶⁸ This study also showed that resolution of chronic GVHD resulted in long-term health outcomes that were comparable to survivors who were never diagnosed with chronic GVHD.

HSCT survivors are also at increased risk for late complications, which include recurrent infections, secondary cancers, cardiac dysfunction, growth failure, weight loss, neurocognitive delay, and other end-organ dysfunction.^{49,50,69} In addition, the inci-

dence of severe or life-threatening chronic health conditions, endocrine complications, or secondary cancers is also higher among HSCT survivors than in non-cancer populations and patients with cancer who are treated conventionally.⁶³ Allogeneic HSCT survivors irradiated at 30 years or younger are at higher risk of developing secondary solid cancers.⁷⁰

These findings highlight the increasingly recognized need for long-term follow-up care that incorporates screening and surveillance of AYA survivors of HSCT.

Adherence to Treatment

Adherence is defined as the extent to which a person's behavior corresponds with agreed recommendations from a healthcare provider. Nonadherence to recommended treatment and follow-up care contributes to poor clinical outcomes in AYA patients with cancer.^{71,72} Failure to keep up with appointments can lead to delayed identification of side effects, complications, or secondary cancers.

Nonadherence to treatment regimens has been an ongoing problem among patients with cancer, and the prevalence of nonadherence has been consistently higher among adolescents compared with younger or older patients with cancer.⁷¹ Nonadherence to oral chemotherapy contributes to reduced treatment efficacy and increased risk of recurrence. Available evidence from clinical trials that have included AYA patients with leukemia and lymphoma suggests that a substantial portion of AYA patients with cancer (27%–63%) have difficulties adhering to their oral treatment regimens.^{71,72}

Nonadherence to other components of cancer treatment (eg, failure to keep appointments for treatment or follow-up, refusing medical examinations, failing to prepare for procedures or therapy) was also identified in AYA patients. Treatment nonadherence in clinical trials can also interfere with adequate evaluation of the efficacy of a given treatment regimen, which in turn can invalidate the results of a clinical trial.

Risk factors for nonadherence among AYA patients include patients' emotional functioning (depression and poor/low self-esteem), personal beliefs (perceived severity of cancer diagnosis and the necessity of intervention), growing independence, competing obligations (school, work, and family), and lack of insurance and appropriate psychosocial

support.⁷³ In a randomized controlled trial, video game intervention significantly improved treatment adherence to prophylactic antibiotics among AYAs with acute leukemia, lymphoma, and soft tissue sarcoma.⁷⁴ Additional studies evaluating the effect of interventions to improve adherence in AYA patients with cancer are needed.⁶

Risk assessment for nonadherence among AYA patients should include consideration of patient maturity, independence, unmet psychosocial and physical needs, and treatment side effects.⁷⁵ For AYAs presumed to be at high risk of nonadherence, implementation of individualized interventions such as additional supportive care resources (eg, social work, psychology, palliative care) to promote adherence may improve outcomes. The patient's personal support system (family and friends) should be mobilized and educated to assist in relieving some of the burdens of care and to positively encourage the patient to maintain adherence to therapy. In the absence of data from studies evaluating the effect of interventions to improve adherence in AYA patients with cancer, findings from studies involving AYA patients with other chronic diseases may be able to be extrapolated to this patient population. For example, a meta-analysis showed that behavioral and multi-component interventions have a moderate effect on improving treatment adherence in children (2–15 years of age) with chronic conditions such as diabetes, asthma, and cystic fibrosis.⁷⁶

NCCN Recommendations to Promote Adherence:

- Educate about the expectations of treatment and explain the patient's responsibility to adhere to treatment. Engage in collaborative treatment decision-making with the AYA patient.
- Provide education and/or guidance about each medication before the start of treatment and every time there is a change in treatment. Review the list of medications as well as dose, purpose, and adverse effects.^{71,72}
- Modify treatment protocol (eg, simplify dosing schedule, change timing and frequency of medication or method of administration), when medically possible, to fit into an AYA patient's lifestyle and normal activities.^{71,72}
- Provide access to systematic and standardized symptom management for side effects related to cancer treatment.^{71,72} See the NCCN Guidelines

for Supportive Care (available at www.NCCN.org).

Impact of Cancer and Its Treatment on Fertility

Infertility is a major consequence of cancer and its treatment in both male and female patients.^{77–80} The impact of cancer treatment on fertility is related to the age of the patient at the time of diagnosis and treatment and depends on the type, duration, and dose intensity of treatment. Alkylating agent–based chemotherapy, high-dose cranial RT that can impair hypothalamic pituitary function, and targeted RT to the uterus, ovaries, or testes are primary risk factors for gonadal dysfunction and decreased fertility in both females and males.^{81–87} Gonadal exposure to low-dose RT can result in oligospermia or azospermia in males. Higher-dose RT is associated with both ovarian and uterine dysfunction in women.

Young women with HL treated with chemotherapy are at risk of developing premature ovarian failure, irrespective of their age at the time of treatment (38% for those diagnosed between 30 and 40 years of age; 37% for those diagnosed between 9 and 29 years of age). The cumulative risks for premature ovarian failure are much higher after alkylating agent–based chemotherapy.^{88,89} In a large cohort of women treated between the ages of 15 and 40 years for HL, the cumulative risk of premature ovarian failure after alkylating agent–based chemotherapy was 60% compared to only 3% or 6% after non-alkylating agent–based chemotherapy.⁸⁹ Independent risk factors for acute ovarian failure include increasing RT doses to the ovaries and exposure to procarbazine and cyclophosphamide at 13 to 20 years of age.⁸² An analysis of 590 women who were diagnosed with HL before age 18 showed that RT to the pelvis was associated with decreased incidence of parenthood (hazard ratio [HR], 0.66; 95% CI, 0.48–0.90; $P=.01$).⁹⁰

Among young women treated with adjuvant chemotherapy for breast cancer, the risk for premature menopause is significantly higher for women older than 35 years with newly diagnosed breast cancer treated with chemotherapy.^{91,92} Similarly, among female survivors of HL diagnosed between 14 and 40 years of age, women who were 22 to 39 years of age at first treatment were at a higher risk of developing premature menopause after treatment compared with younger patients (14–21 years).⁹³ Treatment with MOPP (mechlorethamine, vincristine, procar-

bazine, and prednisone)/ABV (doxorubicin, bleomycin, and vinblastine) significantly increased the risk of ovarian failure. After 10 years of treatment, the actuarial risk of premature menopause was 64% after high cumulative doses ($>8.4 \text{ g/m}^2$) and 15% after low doses ($\leq 4.2 \text{ g/m}^2$) of procarbazine.⁹³

In male patients treated with alkylating agent–based chemotherapy and RT to testes, germ cell dysfunction with resultant infertility is more common than Leydig cell dysfunction and testosterone insufficiency.⁹⁴ Leydig cell dysfunction is characterized by increased plasma concentrations of luteinizing hormone (LH) combined with low levels of testosterone. Germ cell dysfunction is associated with reduced testicular volume, increased follicle-stimulating hormone concentrations, and reduced plasma concentrations of inhibin B. Leydig cell dysfunction occurs at RT doses higher than those associated with germ cell dysfunction. AYA men treated with testicular RT $\geq 20 \text{ Gy}$ are at high risk for Leydig cell dysfunction, whereas testicular RT $\geq 2 \text{ Gy}$ can impair spermatogenesis resulting in permanent azoospermia.⁹⁴ TBI used as part of high-dose conditioning therapy before HSCT can also affect the testes, resulting in permanent infertility in most AYA men.⁵²

Azoospermia is associated with chemotherapy and radiation. Whether it is transient or permanent depends on the type of treatment involved, with radiation and alkylating agents posing the greatest risk for long-term damage.⁹⁵ Azoospermia has been reported in more than 90% of men receiving procarbazine-based chemotherapy regimens such as MOPP and may not resolve over time, resulting in permanent infertility.⁹⁶ Alternatively, the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen has been shown to be less gonadotoxic, with a vast majority of patients regaining normal fertility after completion of treatment.⁹⁷ Cisplatin-based chemotherapy for testicular cancer is associated with temporary azoospermia in most men, with a recovery of spermatogenesis in about 50% to 80% of patients after 2 to 5 years.⁹⁷ RT $> 2 \text{ Gy}$ to the testes, moderate- to high-dose alkylating agent chemotherapy (MOPP > 3 cycles), higher cumulative alkylating agent dose (busulfan $> 600 \text{ mg/m}^2$, cyclophosphamide $> 7.5 \text{ g/m}^2$, or ifosfamide $> 60 \text{ mg/m}^2$), or any alkylating agent combined with RT to testes or TBI are considered risk factors for oligospermia and azoospermia.^{77,85} Pelvic RT and cumulative cyclophosphamide doses

$> 9.5 \text{ g/m}^2$ are associated with a high risk of permanent infertility as seen in male patients with NHL, Ewing sarcoma, and soft tissue sarcomas.^{98,99} Retroperitoneal lymph node dissection is also associated with infertility in men with testicular cancer.¹⁰⁰

The NCCN Guidelines recommend discussing the risks of infertility due to cancer and its treatment with all patients at the time of diagnosis, before starting treatment. This is especially important for patients who will be starting therapies with a high risk of affecting fertility, as described previously.

Fertility Preservation

Fertility preservation is an issue of crucial importance in AYA patients and should be an essential part in the management of their cancer.^{16,52,101–105} The ASCO Clinical Practice Guidelines recommend that providers discuss the options for fertility preservation with all new patients with cancer at diagnosis.¹⁰⁶ Nevertheless, fertility preservation is currently one of the most underprescribed and least implemented services in AYA patients with cancer.^{52,101,107} A study that reviewed 231 records of AYA patients with leukemia/lymphoma, sarcoma, or breast or testicular cancers showed that infertility risk was discussed 26% of the time and fertility preservation options were discussed 24% of the time.¹⁰⁸ However, it is possible that more discussions about infertility occurred without having been documented. Another study that analyzed the electronic medical records of 454 AYA patients at a single cancer center showed that the risk of infertility was discussed with 83% of patients, with women more likely to be informed than men (odds ratio [OR], 3.57; 95% CI, 1.33–9.60; $P = .01$).¹⁰⁹ A study of 146 adolescent boys at risk for infertility due to cancer treatment across 8 different pediatric oncology centers found that only 53.4% attempted to bank sperm, with 43.8% successfully banking. Parent or medical team recommendation was associated with increased likelihood of sperm banking completion.¹¹⁰

Psychosocial providers can assist patients and families in the decision-making process about fertility preservation, particularly when AYA patients are distressed about the potential infertility associated with cancer treatment.¹⁰⁶ The Oncofertility Consortium, a group of clinicians and researchers in the United States, was formed in 2007 to address reproductive barriers facing AYA patients and to identify

research priorities in this area.¹¹¹ Future aims developed during a 2011 meeting are as follows:

- Determine optimal techniques for cryopreservation of reproductive tissue and gametes;
- Further investigate in vitro follicle maturation in primates;
- Investigate AYA patients' psychosocial needs as part of the fertility preservation plan;
- Improve patient-provider communication regarding fertility preservation; and
- Develop and perform multicenter studies, using the preexisting infrastructure of the National Physicians Cooperative.

Options for Females: Ideally, fertility preservation should be initiated before the start of treatment. However, in some situations, when it is impractical or impossible to pursue fertility preservation before starting therapy, it may be appropriate to readdress later in the course of treatment.

Oophorectomy and embryo cryopreservation after in vitro fertilization (IVF) are two established options for fertility preservation in females.¹⁰⁶ Oophorectomy involves surgically displacing the ovaries out of the RT field to minimize ovarian damage and has been shown to preserve ovarian function.¹¹² Embryo cryopreservation after IVF has been highly successful in women younger than 40 years of age.^{52,101} However, this method requires a male partner or sperm donor who is available with short notice. In one study that assessed pregnancy outcomes following embryo cryopreservation, letrozole was used in combination with follicle-stimulating hormone to protect patients with breast cancer against the harmful effects of increased estrogen.¹¹³ Of 33 women, the live birth rate was 45%, with 39% of live births resulting in twins. These rates are not significantly different from those for infertile couples not affected by cancer, except for implantation rate, which was greater in the patients with breast cancer (40.7% vs 26.1%). A little over half (55%) of the embryos were transferred to a gestational carrier, with no significant differences in outcomes (ie, implantation, live birth, twinning rates) between self-transfers and gestational carriers.

Mature oocyte cryopreservation is an alternative for single women, but, like embryo cryopreservation, requires hormone stimulation.^{52,101} Evidence from randomized trials^{114–117} and a meta-analysis¹¹⁸ suggest that IVF with cryopreserved oocytes results in fertilization and pregnancy rates similar to that of fresh

oocytes. Oocyte cryopreservation is no longer considered investigational according to guidelines from the American Society of Reproductive Medicine.¹¹⁹

Ovarian tissue cryopreservation is a promising, but less well studied strategy for female fertility preservation when there is insufficient time for oocyte or embryo cryopreservation and/or the patient is prepubertal. This technique does not require hormonal stimulation, so there is no long delay in initiation of treatment.⁵² Although evidence supporting the effectiveness and safety of ovarian tissue cryopreservation is scarce, a few systematic reviews have supported its use for fertility preservation in cancer patients.^{120,121} This procedure would not be appropriate for some women with cancer, where there is a potential for reintroduction of malignant cells that could occur with grafting. Although ovarian tissue cryopreservation is still considered investigational at some institutions, it may be discussed as an option for fertility preservation, if available. Xenotransplantation of ovarian tissue is currently under investigation.¹²²

Some studies, including randomized trials, have evaluated the role of menstrual suppression with gonadotropin-releasing hormone (GnRH; also known as LH-releasing hormone [LHRH]) agonists to preserve ovarian function during chemotherapy.^{123–131} Some meta-analyses have shown that GnRH agonist may be beneficial for fertility preservation.^{132–134} However, the impact of these meta-analyses are limited by flaws such as only examining women with breast cancer and only including trials that were not adequately powered and did not use blinding and/or a placebo condition.^{135,136} Further, results from earlier meta-analyses were inconsistent, with some showing a potential benefit of GnRH to preservation of ovarian function,^{137–139} while other reviews have been unable to come to this conclusion.^{140,141} Also, limited data are available on the long-term impact of GnRH on preservation of ovarian function,¹³² though a 5-year follow-up analysis of a randomized trial showed that administration of a GnRH agonist does not significantly impact premature ovarian failure or future pregnancy rate.¹³¹ Therefore, though data suggest that menstrual suppression with GnRH agonists may protect ovarian function, further investigation is needed.

Other agents, such as the progestin medroxyprogesterone and oral contraceptives, may be used in women with hematologic malignancies who are at

risk for menorrhagia, but this does not preserve ovarian function.¹⁴² However, caution is needed in endometrial cancer, where progestin therapy has been associated with high rates of cancer recurrence.¹⁴³ This may be prevented by combining metformin with medroxyprogesterone.¹⁴⁴

Options for Males: Semen cryopreservation before the start of treatment is the most reliable and well-established means of preserving fertility in AYA males with cancer.^{52,101} The success of sperm banking may be limited in some patients, such as those with HL and testicular cancer, who may already have azoospermia associated with the disease. Depending on the type of chemotherapy, semen collection may be possible after start of chemotherapy; however, the impact of chemotherapy and RT on the risk of genetic defects in the offspring remains unknown.¹⁴⁵

Cryopreservation and subsequent transplantation of spermatogonial stem cells is experimental but may be an alternative option for some patients in whom semen cryopreservation is not possible.^{52,101} There is limited evidence regarding the efficacy of hormone suppression in reducing the risk of male infertility during chemotherapy.¹⁰⁶

Recommendations for Fertility Preservation: The NCCN Guidelines emphasize that fertility preservation, as well as sexual health and function, should be an essential component of the management of AYA patients, who may be at risk for infertility due to cancer treatments. Options for fertility preservation should be discussed with all patients before the start of treatment and providers should initiate referral to fertility preservation clinics within 24 hours for all patients who choose the option of fertility preservation. Local or institutional grants may be available to provide financial assistance with fertility preservation needs. Follow-up with a fertility specialist after treatment may also be helpful for some patients. Referral to a mental health professional to assist with complex decision-making is recommended.

Females:

- Oophoropexy should be considered for all female patients who will be receiving RT.
- Embryo or oocyte cryopreservation should be discussed, if it is possible to delay treatment long enough for a cycle of oocyte stimulation, espe-

cially for patients with low- and intermediate-risk HL, low-grade sarcomas, and breast cancer.¹¹⁹

- Ovarian tissue cryopreservation may be considered, if available.¹²⁰
- Medroxyprogesterone, oral contraceptives, or GnRH agonists can be used in protocols that are predicted to cause prolonged thrombocytopenia and thus present a risk for menorrhagia.¹⁴²
- Some data suggest that menstrual suppression with GnRH agonists may protect ovarian function.^{128,132,134} However, evidence that menstrual suppression with GnRH agonists protects ovarian function is insufficient, so this procedure is not currently recommended as an option for fertility preservation.

Males:

- Discuss the possibility of sperm banking at diagnosis. AYA patients can use either a local sperm bank or an available online sperm banking kit.
- Oncology centers that treat AYA patients should develop a system for offering sperm banking to all AYA patients in a systematic and patient-centered manner.

Contraception During and After Treatment for Cancer

Male condoms may be safely used by AYA males with cancer.¹⁴⁶ AYA women with cancer have unique contraception needs, and the options are dependent on the type of cancer, its treatment, and treatment-related complications.¹⁴⁷ The NCCN Guidelines recommend discussion about the use of contraception before starting therapy.¹⁴⁷

Long-acting reversible contraception (LARC) with intrauterine devices (IUDs) or implantable contraceptives are more effective than short-term contraceptive methods, which include the use of estrogen and progestin with various delivery systems.¹⁴⁸ LARC has been shown to be superior to short-acting contraceptives in AYA women.^{149,150} In a study of 4,167 women (14–45 years of age), LARC was associated with higher 12-month adherence rates than oral contraceptive pills (86% vs. 55%).¹⁴⁹ In a large, prospective study involving 7,487 women, the contraceptive failure rate was significantly higher for those using oral contraceptive pills, patch, or ring compared to those using LARC (4.55 vs 0.27), and the failure rates among women younger than 21

years were twice as great as in women 21 years of age or older.¹⁵⁰

The Society of Family Planning guidelines recommend the use of IUDs or implantable contraceptives for most women who are receiving treatment for cancer.¹⁵¹ The use of any method of contraception is recommended for women who have been free of cancer for at least 6 months and have no history of hormonally mediated cancers, chest RT, anemia, osteoporosis, or venous thromboembolism (VTE).¹⁵¹ The use of IUDs is considered the preferred first-line contraceptive option for women with a history of breast cancer, although for women treated with tamoxifen, a levonorgestrel-containing intrauterine system (IUS) may be preferable since it has been shown to reduce tamoxifen-induced endometrial changes without increasing the risk of breast cancer recurrence. Levonorgestrel-containing IUS may also be used to minimize menstrual blood loss in women with iron-deficiency anemia.¹⁵¹

Due to the risk of VTE associated with the use of combined hormonal contraceptive methods, the U.S. Centers for Disease Control and Prevention recommend that the use of these contraceptive methods should be avoided in women of childbearing age with active cancer or who have been treated for cancer in the past 6 months.^{152,153}

Management of Cancer During Pregnancy

All women of childbearing potential must receive a pregnancy test before starting therapy. Cancer is diagnosed in about 0.1% of pregnant women and is the second most common cause of maternal death during pregnancy.¹⁵⁴ Cervical, breast, thyroid, and ovarian cancers, melanoma, lymphoma, and leukemia are the most common cancers diagnosed during pregnancy.^{155–158} These are also the most common cancers diagnosed in the AYA population.¹⁵⁹ An analysis of 1963 to 2007 data from the Swedish Multi-Generation Register and the National Cancer Register showed a lower-than-expected number of cancers diagnosed during pregnancy, and a rebound in the number of cases of melanoma, CNS cancers, breast cancer, and thyroid cancer in postpartum women.¹⁵⁸ This rebound may be due to changes in the mammary and thyroid glands being overlooked during the postpartum period. Despite some persisting beliefs, there is no evidence of pregnancy-associated relapse in female survivors of HL.¹⁶⁰

Although research on the prognosis of cancer during pregnancy is limited, a few meta-analyses and systematic reviews have suggested that the prognosis of certain cancers (eg, breast, melanoma, vulvar) may be worse when occurring concurrent with pregnancy compared to the same cancers occurring outside pregnancy.^{161–164} These results may be confounded by factors related to the patients' pregnancy, delays in diagnosis, and differences in treatment decisions, making a definitive conclusion difficult.

Accurate diagnosis of the type and stage of cancer using appropriate imaging studies (ultrasound, chest x-ray, and mammogram) with abdominal shielding and limiting fetal exposure to ionizing radiation is an essential step in the management of cancer during pregnancy.^{165–167} There is insufficient evidence regarding the safety of gadolinium-based contrast agents in pregnant women.¹⁶⁷ Surgery is possible at any time during pregnancy depending on the anatomic location of the tumor, although it may be beneficial to delay surgery, when possible, until after fetus viability.^{165,167} Selection of an appropriate treatment plan for pregnant women is dependent on individual tumor biology and tumor stage, similar to the management of cancer in non-pregnant women. In addition to the disease characteristics in pregnant women, the gestational age of the fetus is a significant factor in the selection of treatment.¹⁶⁵

RT is contraindicated during pregnancy. However, in very rare instances when RT is necessary, it should be delivered in low therapeutic doses (with adequate uterine shielding to minimize fetal exposure) with the goals of controlling maternal cancer and providing the fetus the best chance for survival with normal development.¹⁶⁸ The dose to the fetus can be reduced by using modified RT administration techniques or adding additional shielding between the treatment machine and the patient.¹⁶⁸ Early collaboration among the radiation oncologist, medical physicist, medical and/or surgical oncologist, and obstetrician is essential. The American College of Radiology has developed guidelines with an objective to assist practitioners in identifying pregnancy, preventing unnecessary irradiation of pregnant AYA women, tailoring examinations to effectively manage RT dose, and developing strategies to quantify and evaluate the potential effects of RT delivered to patients who are pregnant.¹⁶⁹ In 2014, an international consensus panel composed of researchers and

clinicians who are experts in treatment of cancer during pregnancy also developed guidelines for RT in women who are pregnant.¹⁶⁶

Chemotherapy should be avoided during the first trimester because of greater risk of teratogenic effects, which include major congenital malformations, impaired organ function, spontaneous abortions, and fetal death.^{167,170–173} Although the use of chemotherapy during the second and third trimesters has not been associated with significant teratogenic effects, it may be associated with low birth weight, preterm labor, and intrauterine growth restriction.^{157,170,172,174–176} However, a multicenter, prospective case-control study of children born to mothers with cancer (129 cases, 129 controls) showed no significant impact of chemotherapy treatment on cognitive, cardiac, and general development of the offspring.¹⁷⁷ Potential benefits and risks of chemotherapy for both the mother and fetus must be carefully evaluated before the start of treatment. Delayed treatment until after fetal maturity, with careful follow-up to rule out disease progression, is a safe option for women diagnosed with early-stage cancers.^{178,179} In some women diagnosed with advanced-stage disease with an urgent need to start chemotherapy in the first trimester, potential benefits and risks of chemotherapy for both the mother and fetus must be carefully evaluated before initiation of treatment.¹⁵⁷ Due to the severe teratogenic effects of methotrexate, it should not be used for the treatment of cancer in women at any stage of pregnancy.¹⁷² Older-generation alkylating agents (eg, procarbazine, busulfan), thalidomide, lenalidomide, pomalidomide, and tretinoin are also considered teratogenic and are contraindicated during pregnancy.¹⁶⁶ The safety and efficacy of hormonal agents and targeted therapies have not yet been evaluated in well-controlled studies including pregnant women.^{165–167,180–182} Currently, the use of such agents in pregnant women is not recommended.

Supportive care for the management of treatment-related side effects should be integrated into treatment planning based on the trimester of pregnancy. Granulocyte-colony stimulating factors for the management of neutropenia and antiemetics for the management of nausea and vomiting have been used in pregnant women without any significant side effects.^{166,181,183,184}

The panel members acknowledged that the management of cancer during pregnancy poses signifi-

cant diagnostic and therapeutic challenges for both the patient and the physician. The guidelines recommend that AYA women diagnosed with cancer during pregnancy require individualized treatment from a multidisciplinary team involving medical, surgical, and radiation oncologists, gynecologic oncologists, obstetricians, and perinatologists as appropriate.^{157,166} Referral to tertiary cancer centers with expertise in the diagnosis of cancer during pregnancy and maternal–fetal medicine and knowledge of the physiologic changes that occur during pregnancy should be strongly encouraged.

Psychosocial and Behavioral Issues

AYA patients diagnosed with and treated for cancer have psychosocial issues that are distinct from those of pediatric and adult patients.^{6,9–12} AYA patients 20 to 29 years of age are significantly less likely to use professional mental health services than teens and older patients 30 to 39 years of age. AYA patients in the 20- to 29-year age group are also significantly more likely to report an unmet need with regard to receiving age-appropriate information about their cancer. Some of the challenges faced by AYA patients and survivors include maintaining an active and independent life, coping with treatment-related side effects and stress, seeking and understanding information, accepting cancer, and maintaining a positive attitude.¹⁸⁵ AYA men and women go through developmental stages marked by rapid changes in cognitive and emotional growth, and these issues need to be considered while delivering developmentally appropriate psychosocial and supportive care to AYA patients.¹⁸⁶

Few measurement tools have been developed to better understand health-related quality of life in AYA patients with cancer.⁶ Palmer et al¹⁸⁷ developed an AYA Oncology Psychosocial Screening Tool to assist clinicians in supporting psychosocial coping during active treatment and promoting healthy post-treatment survivorship in AYA patients. This screening tool has 4 main areas: a distress thermometer, a check list of “areas of concern,” a tick box for information provision, and signatures. Further validation of this tool and its use will help clinicians to improve psychosocial care for AYA patients, regardless of where they receive treatment.¹⁸⁷

Psychosocial needs for AYA patients should be assessed across the following domains: 1) individual function (psychosocial, emotional, and behavioral issues); 2) relationships (family, peers, and health care professionals); and, 3) socioeconomic issues. Age and developmentally appropriate supportive care services and interventions should be used to address each of these domains.

Individual Function

Psychosocial Issues: AYA patients must cope with cancer treatment while accomplishing key developmental tasks such as identity development, including sexual identity; peer involvement; initiating intimate and emotional relationships; establishing autonomy from parents; maintaining personal values; fostering self-esteem and resilience; and independently making decisions about their future that involve education, career, or employment.^{188–191} The impact of diagnosis and treatment of cancer on their physical appearance, sexual development, and sexual function can lead to shame, social isolation, and regressive behaviors if not addressed promptly. Cancer and its often intensive and lengthy treatments put AYA patients at risk for disruptions in their normal activities. Interruptions of school or work due to treatment will have negative consequences for their long-term career opportunities, financial status, and lifetime earnings.¹⁸⁵ During the treatment period, AYA patients should have the opportunity to live as normal a life as possible, continue their education and/or careers, and participate in the many milestones of their lives.¹⁹² Physical and/or occupational therapy may help AYA patients transition back to a lifestyle appropriate for their age group.¹⁹³

Emotional Issues: Cancer-related issues such as confrontation with mortality and loss of fertility can result in significant emotional distress and psychiatric symptoms such as depression and anxiety in AYA patients. These feelings are related to patients' cognitive capacity to understand the severity of their disease while sometimes lacking fully mature cognitive and emotional coping abilities.¹⁸⁵ Psychological distress is significantly greater among AYAs compared with older adults.^{194–198}

In a longitudinal study that assessed the prevalence of psychological distress in 215 AYA patients with cancer (15–39 years of age) during the first year

after diagnosis, distress symptoms exceeded population norms at the time of diagnosis and at 12-month follow-up.¹⁹⁵ In this study, 12% of AYA patients reported clinically significant chronic distress throughout the first 12 months after diagnosis and an additional 15% reported delayed distress.

In addition to distress, depression and anxiety are commonly experienced by AYA cancer survivors. An analysis from the Childhood Cancer Survivor Study (CCSS) showed that survivors of AYA cancer ($n = 2,589$) report higher rates of depression (OR, 1.55; 95% CI, 1.04–2.30) and anxiety (OR, 2.00; 95% CI, 1.17–3.43), compared with their siblings ($n=391$).¹⁹⁹ Another study of 5,341 cancer survivors diagnosed at age 25 or earlier found that survivors were more likely to be prescribed antidepressants compared to age- and gender-matched controls (26.9/1,000 person-years for survivors vs 22.5/1,000 person-years in controls; HR=1.19; 95% CI, 1.12–1.28).²⁰⁰

The need for information, counseling, and practical support was reported in 57%, 41%, and 39% of AYA patients, respectively, at 12 months after the diagnosis of cancer.¹⁹⁷ Kazak et al²⁰¹ reported that intensive cancer treatments during adolescence are associated with inferior psychosocial outcomes and health beliefs in survivors compared with their age-matched peers. Psychological problems are also associated with an increased risk for obesity and poor health behavior, which may increase future risk for chronic health conditions and secondary neoplasms.²⁰²

Behavioral Issues: AYA patients with cancer may engage in risky behaviors (tobacco, alcohol, cannabis, or substance use/abuse) that may impair their health. Older age at cancer diagnosis, lower household income, less education, no pulmonary-related cancer treatment, and no brain RT were independently associated with a statistically significant relative risk of smoking initiation.²⁰³ The risk factors associated with heavy drinking included fair or poor self-assessed health, depression, anxiety, somatization, activity limitations, and cancer-related fears and uncertainty.²⁰⁴ Low perception of susceptibility to late effects, older adolescence compared with early adolescence, and worry were the strongest predictors of substance abuse.²⁰⁵ Although AYA patients may be aware of the complications associated with tobacco, alcohol, cannabis, or substance use/abuse during their treatment, they may not avoid them

throughout their treatment because these habits make them feel normal and like part of their peer group. Clinicians working with this population need to be aware of this and address the issues in a sensitive and confidential manner.^{192,206}

Studies have shown increased rates of mental illness and cognitive impairment among adolescent cannabis users compared with adults with similar usage habits.²⁰⁷ Heavy or regular use of cannabis in adolescents has been associated with impairments in attention, learning, memory, planning, and psychomotor speed. An earlier age of onset of cannabis use exacerbates these adverse effects. If an AYA patient chooses to continue use of cannabis, education on methods for lowering risk of adverse effects is recommended. For example, the patient may be counseled to avoid high tetrahydrocannabinol (THC)-content products, avoid synthetic cannabinoids, choose routes of administration other than inhalation of combusted cannabis, limit frequency of use, and never drive while impaired.²⁰⁸

AYA patients are also vulnerable to sexual and reproductive health complications that should be addressed before, during, and after completion of treatment.¹⁴⁷ Traditional risk-taking behaviors of AYA individuals coupled with a compromised immune system can put AYA patients with cancer and survivors at a greater risk of sexually transmitted infections. See the section on “Contraception During and After Treatment for Cancer” (page 84) for more discussion of appropriate contraception choices for patients with cancer and survivors.

AYA patients have nutritional concerns that are different from those of children and adults, especially among younger patients in this population. Adolescents are dependent on their families for food preparation and may experience peer pressure when eating at school or with friends. Diet/nutrition information has been reported as an unmet need among AYA patients.¹⁰ Nutritional requirements and potential deficits should be evaluated based on the patient’s age.

NCCN Recommendations For Supportive Care Services/Interventions for Psychosocial and Behavioral Issues:

- Provide information about reliable online sources to access developmentally appropriate information related to their cancer. See “Online Resources for AYA Patients and Survivors” in the

complete version of these guidelines, at NCCN.org.

- For all AYA patients, provide counseling around decision-making regarding the risks of infertility associated with cancer and its treatment and the use of fertility preservation and contraception before starting treatment.²⁰⁹
- Because the incidence of sexually transmitted infections peaks among AYAs 15 to 24 years of age, provide preventive health education about sexually transmitted diseases.¹⁹²
- Prescribe and provide nutrition and exercise recommendations for all AYA patients. Refer to a registered dietitian-certified specialist in oncology.²¹⁰
- Consider flexible treatment dates, consultation times, and procedures when possible to enable AYA patients to continue with their treatment without interrupting their school/work or other normal activities.¹⁹²
- Offer psychosocial support and counseling to help alleviate distress. See the NCCN Guidelines for Distress Management (available at NCCN.org).
- Refer AYA patients with cognitive dysfunction or other psychiatric symptoms (eg, depression or anxiety) to a mental health provider and community-based resources serving AYA patients.
- Refer patients with signs, symptoms, and a history of substance abuse or addiction to a risk reduction or substance abuse management program. Refer to smoking cessation program if needed (see NCCN Guidelines for Smoking Cessation (available at NCCN.org)).
- Refer patients experiencing challenges with their faith or belief in a just or fair world to faith-based resources or activities (eg, church youth groups, mentors).^{11,211}
- For those who desire to receive complementary and alternative medicine, refer them to reputable providers of these services.

Relationships

Social, Peer, and Family Relationships: AYA patients often have to endure lengthy hospital stays under the supervision of healthcare providers, resulting in significant isolation from their family members and peer group.¹⁹² Isolation and alienation are common among AYA individuals diagnosed with cancer,

because they often miss out on the life experiences shared by their non-ill peers. Reinforcing relationships with family, peers, and health professionals is an important aspect of life for AYA patients.^{186,212}

Although some studies have identified family support and cohesiveness as important contributors to a survivor's adjustment, others have identified the important role played by same-aged peers (healthy peers as well as other AYA cancer survivors) in helping AYA patients cope with cancer and overcome feelings of loneliness.^{11,186} In one study, AYA patients with cancer (16–22 years of age) identified social support (including family members, friends, healthcare providers, and other patients) as their major coping strategy.²¹³ In another study, some AYA patients and survivors reported that opportunities to meet other young adult survivors were more important than the support they received from family and peers.²⁰⁹

Peer support programs assist AYA patients and survivors in establishing and maintaining relationships with their healthy peers as well as with other AYA patients with cancer, offer opportunities to achieve age-related developmental tasks (building interpersonal and problem-solving skills), and promote positive psychosocial growth.^{209,214} Peer support also provides AYA patients with an opportunity to address areas of shared concern, such as uncertainty about the future, establishing autonomy while being increasingly dependent on family and friends, sexual identity, and infertility, thereby reducing feelings of social isolation.²¹⁴

AYA peer support groups have been developed in a variety of formats, including face-to-face meetings, camp style formats, or online support groups.^{215,216} Social networking groups focused on supporting AYA patients are particularly helpful for exchanging 2 primary types of support—informational and emotional—through providing advice and empathizing with other AYA patients dealing with cancer.²¹⁶ Summer camps and adventure programs where participants are physically challenged have resulted in improvements in self-confidence, independence, and social contacts.^{11,215} Many of the AYA patients may not be interested in conventional cancer support groups but are willing to participate in social networking events involving other AYA patients, survivors, and family members.¹¹ Indeed, studies of AYA patients and survivors indicated that 73% of patients currently receiving therapy and 74% of off-treatment survivors

reported that their needs for retreats and camp programs were unmet.^{217,218}

Communications with Healthcare Professionals:

Communicating information to AYA patients can be challenging, especially because several subgroups within the AYA population have different levels of cognitive and emotional development. Establishing direct communication with the patients on an individual basis, with sufficient sensitivity to each patient's needs and preferences is very important.²⁵ Although some patients prefer not to receive direct communication about their cancer, others may desire to take a more prominent role in the management of their care. For the latter group, information should be provided directly to patients in a developmentally appropriate manner, allowing time to process the information and deliver information in a caring manner.²¹⁹ AYA patients prefer that information about their cancer and cancer-related risks be communicated to them in a manner that is positive, respectful, and non-judgmental.¹⁹² In a pilot project aimed at eliciting the views of AYA patients with cancer, humor, closely followed by expertise and knowledge, was identified as the most important characteristic that patients would like to see in their nurses.²²⁰ Since there is evidence that AYA patients are willing to use the internet to get health information and support, it will also be helpful to provide them with a list of recommended and reliable age-appropriate online sources to access information about their cancer, particularly with regard to treatment and late effects, fertility preservation, mental health counseling, peer support groups, diet, and nutrition.^{215,218,221} See “Online Resources for AYA Patients and Survivors” in the complete version of these guidelines, at NCCN.org.

NCCN Recommendations for Supportive Care Services/Interventions for AYA Patient

Relationships:

- Promote communication between AYA patients and family members (parents, spouse/partners, and siblings).²⁶
- Provide information to family members and partners about psychosocial support and behavioral services to increase awareness of the possible psychosocial issues associated with diagnosis of cancer in AYAs.
- Consider family-based intervention models from pediatrics (eg, parent support groups, Impact of Traumatic Stressors Interview Schedule).¹⁷

- Establish direct communication with individual patients, providing developmentally appropriate information about their cancer, treatment options, and potential side effects, thus reinforcing the importance of AYA involvement in decision-making.^{25,209}
- Some AYA patients prefer not to share information about their cancer with their family in an effort to shield their family members from some of the things they themselves worry about. Therefore, obtain their permission to share information with other family members and encourage completion of a HIPAA release form.
- Provide information about peer support and social networking opportunities and create flexible visiting hours and an environment that will encourage peers to visit AYA patients.¹⁹²
- Encourage completion of a medical power of attorney when appropriate.

Socioeconomic Issues

AYA patients are much more likely to be uninsured or underinsured individuals than adults or children, with many in transition between their parents' insurance and their independent insurance.¹⁷ Young adult survivors of childhood cancers are more likely to report health-related unemployment, lower rates of health insurance coverage, and more difficulties obtaining coverage compared with their siblings.²²² An analysis of 9,353 AYA patients with HL showed that having either public or no health insurance was associated with poorer HL-specific survival compared with patients with private or military insurance (HR, 2.08; 95% CI, 1.52–2.84).²²³ Furthermore, unemployment and lack of health insurance appear to be significant predictors of psychological distress in the childhood cancer survivor population.²²⁴ Uninsured AYA patients are also less likely to participate in clinical trials.⁴¹ As described previously, advanced stage of cancer at diagnosis and lack of health insurance were significantly associated with longer time to cancer diagnosis in AYAs.²²⁵ Greater rates of unemployment and lack of health insurance among AYA patients and survivors are also associated with limited access to long-term follow-up care.¹⁸⁵ Results from the AYA HOPE study, a population-based cohort study of 523 AYA patients with cancer (15–39 years of age at diagnosis from 2007–2009), suggest that lack of health insurance is also associated with

poor health-related quality of life among AYA patients with cancer.²²⁶

AYA patients with employment also experience problems in obtaining affordable health and life insurance due to their pre-existing cancer history.¹¹ Even those with relatively comprehensive insurance may be liable for substantial out-of-pocket expenses related to treatment, such as transportation costs associated with traveling for treatment, accommodations, meals, and childcare as well as expenses not related to treatment.¹¹ AYA patients who are financially independent also have to face an additional burden of loss of income because of their inability to work during treatment. Once the treatment is over, AYA patients with cancer also need long-term follow-up care for monitoring and treatment of late effects.

NCCN Recommendations For Supportive Care Services/Interventions for Socioeconomic Issues:

- Assess AYA patients' health insurance status and provide information on potential sources of coverage (eg, Medicaid, Health Insurance Marketplace, parent's insurance,) and other key elements associated with insurance coverage.
- Educate AYA patients about the benefits for which they may qualify (eg, short- or long-term disability, state disability benefits, Social Security benefits, and public assistance benefits).
- Provide a referral for transportation assistance programs (eg, van ride programs, voucher programs) for AYA patients who must travel to receive treatment. Identify resources for respite care that would be helpful for those with young children.
- Integrate financial assistance for AYA cancer survivors into their survivorship plans.

Palliative and End-of-life Care

Palliative care is interdisciplinary care of patients with life-threatening illnesses, malignant as well as non-malignant. The goal of palliative care in patients with cancer is to control symptoms, relieve emotional and physical suffering from adverse effects of treatment, and improve quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies.^{227,228} See the NCCN Guidelines for Palliative Care (available at NCCN.org).

Palliative care services for AYA patients should be provided by a multidisciplinary team with expertise in understanding the psychosocial, emotional, developmental, and financial issues that are unique to this age group.^{227,229} Introduction of palliative care for symptom management and psychosocial support should occur before the patient's condition is considered "palliative" in order to provide the best possible care.²³⁰ Palliative care is appropriate even when patients are being treated with curative intent, and there is growing consensus that AYA patients should have access to palliative care services from the time of diagnosis until the time of death or cure.²³⁰ Patients, caregivers, and healthcare professionals should be taught that palliative care is an integral part of their comprehensive cancer care.²²⁹ AYA patients usually do not make decisions in isolation. Although some AYA patients have the ability to make life and death decisions independently, many are either not the primary decision maker or they rely intensely on input from parents, spouses, significant others, and other family members.²²⁷ Palliative care services should also consider the psychosocial needs of the patient's family, friends, and caregivers.²³⁰ Patients' goals, dreams, and desires to leave a legacy are important considerations to address.²²⁹

End-of-life care involves the palliation of symptoms, management of delirium, existential distress, discussion about the place of death, and support of family.^{227,229} It is imperative for healthcare professionals not to assume that AYA patients may be less inclined to discuss death and other end-of-life issues.²²⁷ In an exploratory study of 50 adolescent patients (15–21 years of age) with and without chronic illnesses, adolescents were willing to discuss end-of-life decision-making by taking part in a one-on-one survey administered by a researcher.²³¹ The quality of life of AYA patients should be heeded by the care team.²²⁹ During palliative and end-of-life care, AYA patients may be able to and wish to continue to en-

gage in day-to-day activities, even if some activities are in discord with medical advice (eg, participating in strenuous physical activity).

Discussion about end-of-life preferences should begin at the time of starting treatment, but details should be individualized according to the preferences of the AYA patient and family.²³² A chart review regarding end-of-life care in 663 AYA patients showed that these patients receive medically intensive therapy at about the same rates as older patients, indicating a need for better understanding of care preferences in these patients.²³³ AYA patients' opinions about end-of-life care vary across this age group. Exploring individual preferences for end-of-life care and providing interventions specific to the needs of this patient population could significantly improve end-of-life care.^{232,234} In one retrospective review, a significant number of adolescents dying of cancer felt that discussions about end-of-life occurred very close to death, allowing very little time to psychologically prepare for death.²³⁵ 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.²²⁷ An advance care planning document is recommended for terminally ill AYA patients with metastatic cancer.^{232,236} Ongoing psychosocial support is extremely important during the transition to end-of-life care.

Summary

AYA patients with cancer should be recognized as a distinct population that has unique medical and psychosocial needs. It is important for physicians to identify issues specific to the AYA population and recommend appropriate interventions with the aim of improving clinical outcomes. Most importantly, all AYA patients should have access to age-appropriate supportive care as well as medical subspecialty services appropriate for their cancer diagnosis.

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Individual Disclosures for Adolescent and Young Adult Oncology Panel				
Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Lynda Beaupin, MD	None	Spectrum Pharmaceuticals	None	7/6/17
Virginia F. Borges, MD, MMSc	None	None	None	1/6/16
Scott C. Borinstein, MD, PhD	None	Rally Foundation; and St Baldrick's Pediatric Cancer Research Foundation	None	8/31/17
Rashmi Chugh, MD	AAI, LLC; Biomarín Pharmaceutical; Eli Lilly and Company; Epizyme, Inc.; MabVax Therapeutics, Inc.; Morphotek Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	EMD Serono, Inc.; and Epizyme, Inc.	None	8/31/17
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Shira Dinner, MD	Astellas Pharma US, Inc.; FLX Bio, Inc.; FORMA Therapeutics; Juno Therapeutics; and MedImmune Inc.	None	None	8/30/17
Jeanelle Folbrecht, PhD	None	None	None	11/20/17
A. Lindsay Frazier MD, ScM	Seattle Genetics, Inc.	Seattle Genetics, Inc.	None	2/6/17
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Diane Puccetti, MD	None	None	None	8/8/17
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Margaret von Mehren, MD	Arog Pharmaceuticals, Inc.; Arqule, Inc.; Blueprint Medicines Corporation; CytRx Corporation; Immune Design; Karyopharm Therapeutics Inc.; and SARC	Deciphera Pharmaceuticals, Inc.; and Janssen Pharmaceutica Products, LP	None	3/25/17
Daniel S. Wechsler, MD, PhD ^a	Karyopharm Therapeutics Inc.	Hyundai Hope on Wheels; Pablove Foundation; and St. Baldrick's Foundation	None	3/7/17
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Nicholas Yeager, MD	None	None	None	8/21/17

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^aThe following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty conflict:

Robert Goldsby, MD: Pfizer Inc.

Daniel S. Wechsler, MD, PhD: American Board of Pediatrics; Subboard on Pediatric Hematology Oncology; American Society of Pediatric Hematology; and Oncology Board of Trustees