Overview

Over the past 20 years, advances in cancer treatment have significantly improved survival rates for young children and older adults, but no significant improvement has been seen in the treatment of adolescent and young adult (AYA) patients with cancer (diagnosed between 15 and 39 years).\(^1\) One of the main reasons for the lack of improvement in outcomes is that AYA patients have a low rate of participation in clinical trials.\(^1\)–\(^3\) In the United States, approximately 10% of patients aged 15 to 19 years...
and 1% to 2% of patients aged 20 to 39 years are enrolled in clinical trials. In addition to the low rate of participation in clinical trials, several other factors also contribute to the poor outcome in AYA patients with cancer, such as differences in disease biology, lack of consistency in treatment approaches, poor compliance with or intolerance of therapy, lack of health insurance, delays in diagnosis, and physician’s lack of familiarity with cancer in the AYA population.

The biology, epidemiology, and clinical outcomes affecting AYAs with cancer are usually different from those of older individuals with cancer. In addition, the genetic, physiological, and pharmacologic changes associated with the AYA population may impact AYAs’ ability to tolerate cancer therapy and response to treatment. 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. Fewer evidence-based data are available to guide the treatment of these patients. AYA patients diagnosed with cancer should be recognized as a distinct age group that has unique medical and psychosocial needs. The distinct biology of disease as well as age-related issues in the AYA population should be considered in the treatment decision-making process.

The AYA patient is generally defined as an individual 15 to 39 years of age at initial cancer diagnosis, although variations may be appropriate...
DEFINITION OF THE ADOLESCENT AND YOUNG ADULT ONCOLOGY POPULATION

The NCI SEER database defines adolescent and young adult (AYA) oncology patients as those diagnosed at 15-29 years of age.\(^a\) Subsequently, NCI's AYA Oncology Progress Review Group defines AYA as a patient diagnosed at 15-39 years of age.\(^b\) In these NCCN Guidelines, AYAs are defined as patients 15-39 years of age at the time of initial cancer diagnosis.

PURPOSE OF THE NCCN GUIDELINES FOR AYA ONCOLOGY

- These guidelines were developed as supportive care guidelines and not as treatment guidelines. The purpose of the guidelines is to increase awareness of unique issues in AYA oncology, and to identify issues and recommend interventions unique to the AYA population. In addition, these guidelines will identify resources available to the AYA population, include appropriate tabular materials, and make recommendations per patient management.
- AYA patients diagnosed with cancer should be recognized as distinct age groups that have unique medical and psychosocial needs. The frequency of distribution of cancer types is dramatically different across the age spectrum of the AYA population.\(^c\)
- The distinct biology of disease and other age-related issues in the AYA population (fertility, long-term side effects, insurance/financial issues, transportation to clinic appointments, child care, psychosocial support, and adherence to therapy) should be considered in the treatment decision-making process.
- The goal of these guidelines is to identify issues specific to the AYA population; recommend interventions unique to the AYA population; educate physicians regarding the prevalence of cancer in AYA and its long-term consequences; identify special considerations related to cancer management in AYA patients with the aim of improving treatment tolerance, compliance, and clinical outcomes; and promote participation in clinical trials.
- Participation in clinical trials should be strongly encouraged in the AYA population.

### SCREENING, ASSESSMENT, AND EVALUATION

AYA patients are usually tolerant of intensive therapies. Treatment approaches will vary depending on diagnosis.\(^d\)

\(^a\)Bleyer A, O'Leary M, Barr R, Ries L. Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival: 1975-2000. National Cancer Institute, NIH Pub. No. 06-5767. Bethesda, MD 2006.


\(^c\)For age-specific incidences rates of cancer by age group and sex in the AYA population, see Table 2 (page 1130).
SCREENING, ASSESSMENT, AND EVALUATION

AYA patients are usually tolerant of intensive therapies. Treatment approaches will vary depending on diagnosis.

Strongly consider a referral for treatment at a cancer center with expertise in treatment of AYAs with cancer and have access to clinical trials for AYAs.

Does this patient need emergency therapy within 24 hours?

YES

Stabilize with appropriate interventions

See Comprehensive Assessment (page 1116) and Socioeconomic Issues (page 1122)

NO

\[d\] See Definition of AYA Population (previous page).

\[e\] These centers provide a multidisciplinary approach involving a 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, smoking, and substance abuse.
• Provide age-appropriate information related to cancer
  See Online Resources for AYA Patients and Survivors (page 1128)
• Discuss risks for fertility and fertility preservation before the start of therapy
  See Fertility/Endocrine Considerations (page 1119)

• Psychosocial assessment
  ▶ See psychosocial/behavioral considerations
    ▷ Individual (page 1120)
    ▷ Relationships (page 1121)
    ▷ Socioeconomic Issues (page 1122)
  ▶ See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Distress Management*

• Genetic and familial risk assessment (within 2 months after the start of therapy)
  ▶ 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
    ▷ 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 AYA with wild-type gastrointestinal stromal tumors (GIST) (lacking KIT or PDGFRA mutations)
    ▷ FAP-associated desmoid tumors (aggressive fibromatosis)
      See NCCN Guidelines for Colorectal Cancer Screening*
  ▶ Risk factors for malignant peripheral nerve sheath tumors
    ▷ Germline mutations in neurofibromatosis type I (NF1)

*To view the most recent version of these guidelines, visit NCCN.org.
The spectrum of cancer types that affect the AYA population is unique and different from cancer types that affect the pediatric and older populations. When homicide, suicide, and unintentional injury are excluded, cancer is the leading cause of death in this age group. The most common cancers by histologic subtype and by sex are listed below:\(^g,h\)

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Ages 15-39</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>20.4</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>14.6</td>
</tr>
<tr>
<td>Melanoma</td>
<td>9.5</td>
</tr>
<tr>
<td>Carcinoma of cervix and uterus</td>
<td>9.1</td>
</tr>
<tr>
<td>HL</td>
<td>3.7</td>
</tr>
<tr>
<td>Carcinoma of colon and rectum</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Gonadal germ cell tumors</td>
<td>10.1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>5.5</td>
</tr>
<tr>
<td>NHL</td>
<td>4.7</td>
</tr>
<tr>
<td>Carcinoma of colon and rectum</td>
<td>3.6</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>2.9</td>
</tr>
</tbody>
</table>

\(^f\)The appropriate location of care and the treatment varies with the type of cancer. Consider referral to medical centers with expertise in treating AYA patients with cancer.

\(^g\)Rates are per 100,000.

TREATMENT-RELATED ISSUES

• AYA patients are usually tolerant of intensive therapies compared to older patients
  ▶ Dose intensity and dose density are associated with improved outcomes\(^1\)
  ▶ See NCCN Guidelines for Myeloid Growth Factors* for growth factor support
• Dose reductions are often based on 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 for certain medications associated with irreversible organ
    damage may be essential when certain life time exposure is encountered
    ▶ Anthracycline-based chemotherapy (cardiac dysfunction)
    ▶ Eppidophyllotoxins (secondary acute myeloid leukemia [AML])
    ▶ Cisplatin (hearing impairment)
    ▶ Ifosfamide (renal dysfunction)
• Maximum cumulative dosing parameters are often established for a patient to reduce the risk of
  significant irreversible damage

Dose schedules

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*
  ▶ Intensive screening is recommended for the following treatment-related toxicities:
    ▶ Cardiac toxicity: regular echocardiograms (EKG) to monitor cardiac toxicity associated with
      anthracycline-based chemotherapy
    ▶ 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

*To view the most recent version of these guidelines, visit NCCN.org.

FERTILITY/ENDOCRINE CONSIDERATIONS

- Fertility preservation should be an essential part of the management of AYAs with cancer.
- Discuss the risk of infertility due to cancer therapy with all patients at the time of diagnosis.
  - Women are at risk for premature ovarian failure from chemotherapy.
  - Men are at risk for azoospermia following therapy, which may or may not resolve over time.
- Refer to online Fertile Hope Risk Calculator: http://www.fertilehope.org/to ol-bar/risk-calculatofm

Males
- Offer sperm banking for all patients at the time of diagnosis.
- Suggest a local sperm bank, or
- Suggest a Live:On kit (http://www.liveonkit.com)

Females
- Discuss the possibility of embryo cryopreservation.
- Initiate if provider deems that therapy can be delayed long enough for a cycle of oocyte stimulation (ie, for low- and intermediate-risk Hodgkin lymphoma and low-grade sarcomas).
- Oophoropexy: Ovaries may be surgically moved away from the planned radiation field, either during cancer surgery or in a separate procedure.
- Oocyte cryopreservation: This occurs most frequently in the context of clinical trials.
- Menstrual suppression: Does not "protect the ovaries".
- Medroxyprogesterone or oral contraceptives may be used in protocols that are predicted to cause prolonged thrombocytopenia and present a risk for menorrhagia.


The 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. To view the most recent version of these guidelines, visit NCCN.org.
### Psychosocial/Behavioral Considerations

#### Assessment

<table>
<thead>
<tr>
<th>Individual</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>Cognitive function</td>
</tr>
<tr>
<td></td>
<td>Emotional issues (See NCCN Guidelines for Distress Management*)</td>
</tr>
<tr>
<td></td>
<td>Evaluate for other psychiatric symptoms, depression, and anxiety</td>
</tr>
<tr>
<td></td>
<td>Living status</td>
</tr>
<tr>
<td></td>
<td>Alone</td>
</tr>
<tr>
<td></td>
<td>Spouse/partner</td>
</tr>
<tr>
<td></td>
<td>Parents</td>
</tr>
<tr>
<td>Behaviors</td>
<td>Adherence to therapy</td>
</tr>
<tr>
<td></td>
<td>Involvement/interruption of school/work</td>
</tr>
<tr>
<td></td>
<td>Tobacco, alcohol, or substance abuse</td>
</tr>
<tr>
<td></td>
<td>Sexual behavior/risk/concerns</td>
</tr>
<tr>
<td></td>
<td>Dietary needs</td>
</tr>
<tr>
<td></td>
<td>Exercise needs</td>
</tr>
<tr>
<td></td>
<td>Existential/spiritual issues</td>
</tr>
</tbody>
</table>

#### Supportive Care Services/Interventions

- 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.
- Offer psychosocial support and counseling to help alleviate distress. See NCCN Guidelines for Distress Management.*
- Adherence 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 AYA patients with signs, symptoms, and a history of substance abuse or addiction to a risk reduction or substance abuse management program.
- Provide health education about sexually transmitted infections, diet, and exercise.
- For all AYA patients, provide counseling regarding the risks of treatment-related infertility and discuss options for fertility preservation prior to the start of therapy. See Fertility/Endocrine Considerations (page 1119).
- 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).

*To view the most recent version of these guidelines, visit NCCN.org.
PSYCHOSOCIAL/BEHAVIORAL CONSIDERATIONS

ASSESSMENT

- Family status
  - Interaction and relationship with parents
  - Interaction and relationship with spouse/partner
- Peer relationships
- Participation in community and social activities (e.g., religious organizations, clubs, athletics/recreation, music, youth groups)
- Communications with health care professionals
  - Decision-making preferences: parents, clinical, and/or self
  - Information and communication preferences (e.g., parents)

EVALUATION

- Emotional issues
- Adherence to therapy
- Involvement/interruption of school/work
- Tobacco, alcohol, or substance abuse
- Sexual behavior/risk/concerns
- Dietary needs
- Exercise needs
- Existential/spiritual issues

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.
- Family-based intervention models from pediatric studies may have utility for AYAs:
  - Parent support groups
  - AYA support groups
  - Social and recreational programs
  - Psychoeducational programs
- Provide information about peer-support groups to assist AYAs establishing and maintaining relationships with their normal peers as well as with other AYAs with cancer. See Online Resources for AYA Patients and Survivors (page 1128):
  - Face-to-face meetings
  - Camp and retreat programs
  - Online support groups
- Create flexible visiting hours and an environment that will encourage peers to visit AYA patients.
- Health care professionals should establish direct communication with individual patients:
  - Reinforce the importance of AYA involvement in decision-making
  - Provide age-appropriate information about their cancer, treatment options, and potential side effects
  - Ask for permission to share information with family members
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
Socioeconomic issues

• Insurance availability and security
  • Employer-provided
  • Parent’s insurance
  • 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
• Desires for complementary and alternative medicine (CAM)

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/or food stamps.
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).
Refer to reputable providers of CAM services.
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 (page 1128).

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.

AYA cancer survivor

SURVIVORSHIP

SELECTED EXPOSURES

SCREENING RECOMMENDATIONS

(See Screening Recommendations, pages 1125 and 1126)

• Cranial or craniospinal radiation
• Neuroendocrine axis screening
• Neuropsychological evaluation

• Chest radiation
• Females: see breast cancer screening
• Thyroid screening
• Cardiovascular risk assessment and screening
• Screening for cardiomyopathy
• Screening for valvular heart disease
• Pulmonary screening

• Abdominal or pelvic radiation
• Colorectal cancer screening
• Assessment of gonadal function
• Screening for kidney or bladder disease

• Alkylating agents
• Screening for kidney or bladder disease
• Assessment of gonadal function
• Screening for t-AML or myelodysplasia
• Pulmonary screening (for selected agents)
• Screening for cardiomyopathy

• Anthracyclines
• Screening for cardiomyopathy
• Screening for t-AML or myelodysplasia

• Bleomycin
• Pulmonary screening
• Cardiovascular risk assessment
• Screening for kidney and/or bladder disease
• Audiological evaluation
• Screening for t-AML or myelodysplasia

• Cisplatin

• Epipodophyllotoxins
• Screening for t-AML or myelodysplasia

AYA cancer survivorship occurs after successful completion of therapy.
DISEASE-SPECIFIC ISSUES RELATED TO AGE

Acute lymphoblastic leukemia (ALL)
- See NCCN Guidelines for ALL*

Bone and soft tissue sarcomas
- See NCCN Guidelines for Bone Cancer* and NCCN Guidelines for Soft Tissue Sarcoma*
- Rhabdomyosarcoma
  - Uncommon outside of the pediatric population; should be referred to an institution with experience in the management of rhabdomyosarcoma

Colon cancer
- Higher incidence of mucinous histology
- More often right-sided
- Higher incidence of signet ring cells and microsatellite instability (MSI)
- More advanced stage at diagnosis
- Lower incidence of KRAS mutations
- Decreased incidence of chromosomal instability
- Consider mismatch repair gene deficiency in these patients
- Increased risk for additional malignancies

Melanoma
- Melanocytic tumors of uncertain malignant potential (MELTUMP) are more frequently seen in younger patients and when suspected, referral to a pathologist with expertise in atypical melanocytic lesions is recommended.
- Principles of pathology for younger patients with consideration to additional testing comparative genomic hybridization (CGH) or fluorescent in situ hybridization (FISH) may be useful to detect the presence of selected gene mutations for histologically equivocal lesions. See NCCN Guidelines for Melanoma.*
- Sentinel lymph node biopsy
  - Higher yield in AYA population
- Surgical margins have not been established for patients < 18 years of age because they were not included in the trials. www.

*To view the most recent version of these guidelines, visit NCCN.org.
SCREENING RECOMMENDATIONS FOR AYA SURVIVORS

The following screening recommendations are adapted from the treatment exposure-based Children's Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.

- The recommendations represent only key aspects; for more detail, refer to the Web site http://survivorshipguidelines.org
- The COG Guidelines are based on exposures used in the treatment for pediatric cancer. As such, the recommendations are applicable to many survivors of cancers that span across adolescence and young adulthood, such as acute leukemias, Hodgkin and non-Hodgkin’s lymphomas, medulloblastomas, and sarcomas. In addition, because the treatment exposures for some young adult cancers, such as male germ cell tumors, are similar to pediatric cancer treatments (eg, cisplatin, bleomycin, abdominal irradiation), the recommendations may be applicable. In contrast, the COG recommendations are generally not applicable to survivors of typical adult carcinomas occurring during young adulthood, such as breast, colorectal, and ovarian cancers.
- The risk for many late effects may be influenced by family history, lifestyle behaviors, and comorbid health conditions. The following recommendations are based on the treatment exposure; timing and intensity of screening may be adapted based on additional risk factors.
- Most survivors will have multiple treatment exposures, and therefore may have multiple screening needs.

Neuroendocrine axis screening (selected outcomes)

- Growth hormone deficiency
  - High-risk population: radiation dose to hypothalamic-pituitary-adrenal (HPA) axis > 18 Gy
  - Screening recommendation: height, weight, and body mass index every 6 months until growth is completed then yearly. Note: most AYA patients will have attained (or nearly attained) final height; the significance and management of growth hormone status among survivors who attained their final height is controversial
  - Consider endocrine consultation for height below the third percentile on the growth curve, drop of less than second percentile rankings on the growth chart
- Central hypothyroidism
  - High-risk population: total radiation dose to HPA axis > 40 Gy
  - Screening recommendation: thyroid-stimulating hormone (TSH) and free T4, yearly
- Gonadotropin deficiency
  - High-risk population: total radiation dose to HPA axis > 40 Gy
  - Screening recommendation: FSH, luteinizing hormone (LH), and testosterone (males), and FSH, LH, and estradiol (females) as clinically indicated; semen analysis (males) as requested by patient or for evaluation of fertility
- Central adrenal insufficiency
  - High-risk population: total radiation dose to HPA axis > 40 Gy
  - Screening recommendation: 8:00 AM serum cortisol, yearly for at least 15 years after treatment and as clinically indicated

Neuropsychological evaluation

- Severe neurocognitive deficits are uncommon in survivors of AYA cancer, including CNS tumors. However, subtle deficits in executive function, sustained attention, memory, and processing speed may occur with higher-dose cranial radiation (> 18 Gy)
- Screening recommendation: in patients with evidence of impaired educational or vocational progress, formal neuropsychological evaluation is recommended

Breast cancer screening (females)

- High-risk population: chest radiation > 20 Gy before the age of 30 years
- Screening recommendation: breast MRI and mammogram yearly, starting at 25 years of age or at 8 years after radiation, whichever occurs last

Cardiovascular risk assessment and screening

- High risk populations: TBI, mediastinal/chest radiation > 20 Gy
- Screening recommendation: measure blood pressure and body mass index yearly; fasting glucose, lipid profile every 2 years
- Screening for ischemic coronary artery disease remains controversial; consider cardiology consultation (5-10 years after radiation) in patients who received > 40 Gy of chest radiation

Screening for cardiomyopathy/asymptomatic heart failure

- High-risk population: cumulative anthracycline dose > 300 mg/m²; chest radiation > 30 Gy; combination of anthracycline and chest radiation
- Screening recommendation: EKG (or MUGA scan) every 1-2 years (Note: frequency of testing is dependent on both age at time of exposure and dose of exposure. The frequency of testing has not been established for breast cancer survivors treated with lower cumulative doses of anthracyclines.)

Screening for valvular heart disease

- High-risk population: chest radiation > 30 Gy
- Screening recommendation: EKG every 1-2 years

Continued on page 1126
SCREENING RECOMMENDATIONS FOR AYA SURVIVORS  (Cont. from page 1125.)

Pulmonary screening
• High-risk population: chest radiation > 15 Gy (or radiation to large volume of lung), TBI (> 6 Gy in single fraction or > 12 Gy fractionated), bleomycin > 400 U/m², combination of chest radiation and bleomycin, and selected alkylating agents (busulfan > 500 mg, carmustine > 600 mg/m²)
• Screening recommendation: chest radiograph and pulmonary function tests (including diffusion lung capacity for carbon monoxide [DLCO] and spirometry) as a posttherapy baseline and then as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction

Thyroid screening
• Thyroid disorders: hypothyroidism (very common), thyroid cancer (common), and hyperthyroidism (uncommon)
• High-risk population: radiation field includes the thyroid gland (see neuroendocrine axis screening for high-dose cranial radiation)
• Screening recommendation: TSH and thyroid/neck exam, yearly

Colorectal cancer screening
• High-risk population: abdominal or pelvic radiation > 30 Gy
• Screening recommendation: colonoscopy starting at 35 years of age or at 10 years after radiation, whichever occurs last

Screening for kidney and/or bladder disease
• Renal insufficiency and secondary renal/renovascular hypertension
  ▶ High-risk population: radiation > 10 Gy, combination of radiation with nephrotoxic agents (eg, cisplatin, ifosfamide, aminoglycosides, amphotericin, immunosuppressants)
  ▶ Screening recommendation: post-therapy baseline blood urea nitrogen (BUN), creatinine, Na, K, Cl, CO₂, Ca, Mg, PO₄; repeat as clinically indicated; measure blood pressure yearly, and urinalysis yearly
• Hemorrhagic cystitis/bladder fibrosis
  ▶ High-risk population: cyclophosphamide > 3 g/m², pelvic radiation > 30 Gy
• Screening recommendation: urinalysis, yearly
• Bladder cancer
  ▶ High-risk population: cyclophosphamide combined with pelvic radiation
  ▶ Screening recommendation: urinalysis, yearly

Assessment for gonadal function
• Males
  ▶ Infertility
    ◦ High-risk population: moderate- to high-dose alkylating agent chemotherapy (eg, MOPP > 3 cycles; busulfan > 600 mg/m², cyclophosphamide cumulative dose > 7.5 g/m² or as conditioning for hematopoietic cell transplant, ifosfamide cumulative dose > 60 g/m²), TBI, testicular irradiation > 2 Gy, and any alkylator combined with testicular irradiation or TBI
    ◦ Screening recommendation: semen analysis as requested by patient or for evaluation of infertility; periodic evaluation over time is recommended as resumption of spermatogenesis can occur up to 10 years posttherapy
  ▶ Leydig cell dysfunction
    ◦ High-risk population: testicular irradiation > 20 Gy
    ◦ Screening recommendation: testosterone as clinically indicated in patients with clinical signs and symptoms of testosterone deficiency
• Females
  ▶ Infertility (acute ovarian failure or premature menopause)
    ◦ High-risk population: moderate- to high-dose alkylating agent chemotherapy (eg, MOPP > 3 cycles, Busulfan > 600 mg/m², cyclophosphamide cumulative dose > 7.5 g/m² or as conditioning for hematopoietic cell transplant, ifosfamide cumulative dose > 60 g/m²), TBI, and abdominal and/or pelvic radiation
    ◦ Screening recommendation: FSH, LH, estradiol as indicated in patients with irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency

Screening for t-AML or myelodysplasia
• High-risk populations: episodophyllotoxins, alkylating agents, cisplatin, and/or anthracyclines
• Screening recommendation: CBC/differential yearly, up to 10 years after exposure

Audiological evaluation
• High-risk population: cisplatin > 360 mg/m², radiation involving the ear > 30 Gy, and combination of cisplatin and cranial/ear radiation
• Screening recommendation: audiology testing as a posttherapy baseline and then as clinically indicated for signs and symptoms of hearing loss
PALLIATIVE CARE/END-OF-LIFE CONSIDERATIONS

Palliative care was commonly called “end-of-life care” but it is now accepted as a treatment to control symptoms, and reduce emotional and physical suffering at any stage of a life-threatening disease. Referral to palliative care is still appropriate when patients are being treated with curative intent. The WHO definition of palliative care includes palliative care being initiated at diagnosis. A palliative care team should involve a multidisciplinary team with expertise in understanding the psychosocial, emotional, and developmental issues that are unique to the AYA population. See NCCN Guidelines for Palliative Care (to view the most recent version of these guidelines, visit NCCN.org).

Four main ideas of palliative care needs for AYA population: ¹
• Psychosocial needs

See Psychosocial/Behavioral Considerations (page 1121)
- Psychosocial needs of the patient
  - Needs depends on maturity, and level of independence (loss of new-found independence)
  - Peer support: facilitate peer relationships and interaction with patient’s normal peers and other AYAs with cancer
  - Provide physical space in a clinic, hospital, etc for social interactions, Web-based peer support, and social networking
  - Provide age-appropriate professional psychosocial support services
- Psychosocial needs of family and friends
  - Grief from loss of loved ones begins even before death. Provide family members and friends with information about palliative care services
  - Provide regular counseling and psychosocial support
- Psychosocial needs of the professional caregivers
  - There is a high rate of “burnout” among palliative caregivers
  - Provide support for debriefing and to maintain a balance between home and work

• Introducing palliative care
  - Lack of communication about illness trajectory is a barrier to transition to palliative care.
  - Introduction of palliative care for symptom management and psychosocial support should occur before the patient is considered “palliative” to provide the best possible care for the patient.
  - Efforts should be made to normalize palliative care involvement without providing a negative connotation of terminal care.

• Resources required

See Psychosocial /Behavioral Considerations (page 1122)
- Insurance availability and security: Provide information about Medicaid, social security, and disability insurance
- Provide flexibility in the health care system for patients to maintain “normalcy”
- Evidence-based guidelines in AYA palliative care are limited and need to be developed
- Advocacy
  - AYA-specific advocacy groups need to be developed at the state/national/international level to increase awareness.
  - It is important to create an AYA team that includes palliative care to improve early referrals, research, and patient-centered care.

End-of-life considerations
- AYAs understand that death is permanent and irreversible. 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
- Adolescents indicate a preference for dying at home, yet 80% have died in a hospital.⁵,⁶
- Palliative care physicians should facilitate discussion about end-of-life care issues, such as nutrition/hydration, sedation treatment cessation, and place of death.²
- An advanced care planning document may be appropriate and helpful for terminally ill AYA patients with metastatic cancer.⁷

ONLINE RESOURCES FOR AYA PATIENTS AND SURVIVORS

<table>
<thead>
<tr>
<th>Website</th>
<th>URL</th>
</tr>
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<tbody>
<tr>
<td>15-40 Connection</td>
<td><a href="http://www.15-40.org/">http://www.15-40.org/</a></td>
</tr>
<tr>
<td>AYA Cancer Patients and Survivors: Teenage, Adolescent and Young Adult</td>
<td><a href="http://www.facebook.com/ayacancer">http://www.facebook.com/ayacancer</a></td>
</tr>
<tr>
<td>Cancer care Support Groups</td>
<td><a href="http://www.cancercare.org/support_groups">http://www.cancercare.org/support_groups</a></td>
</tr>
<tr>
<td>First Descents (Free outdoor adventure programs for young adult cancer fighters and survivors ages 18 to 39)</td>
<td><a href="http://firstdescents.org">http://firstdescents.org</a></td>
</tr>
<tr>
<td>Focus under Forty</td>
<td><a href="http://university.asco.org/focusunder40">http://university.asco.org/focusunder40</a></td>
</tr>
<tr>
<td>Gilda’s Club</td>
<td><a href="http://wwwgildasclub.org">http://wwwgildasclub.org</a></td>
</tr>
<tr>
<td>I’m Too Young For This! Cancer Foundation</td>
<td><a href="http://stupidcancer.com/about/index.shtml">http://stupidcancer.com/about/index.shtml</a></td>
</tr>
<tr>
<td>Imerman Angels (One-on-One Cancer support-Connecting Cancer Fighters, Survivors and Caregivers)</td>
<td><a href="http://www.imermanangels.org">http://www.imermanangels.org</a></td>
</tr>
<tr>
<td>LIVESTRONG Young Adult Alliance</td>
<td><a href="http://www.livestrong.org/LIVESTRONG-Young-Adult-Alliance">http://www.livestrong.org/LIVESTRONG-Young-Adult-Alliance</a></td>
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<tr>
<td>Mass Kickers Foundation</td>
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<tr>
<td>National Coalition for Cancer Survivorship</td>
<td><a href="http://www.canceradvocacy.org">http://www.canceradvocacy.org</a></td>
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<td>Planet Cancer</td>
<td><a href="http://www.planetcancer.org">http://www.planetcancer.org</a></td>
</tr>
<tr>
<td>Surviving and Moving Forward: The SAMFund for Young Adult Survivors of Cancer</td>
<td><a href="http://www.thesamfund.org">http://www.thesamfund.org</a></td>
</tr>
<tr>
<td>Teens Living With Cancer</td>
<td><a href="http://www.teenslivingwithcancer.org">http://www.teenslivingwithcancer.org</a></td>
</tr>
<tr>
<td>The Jack &amp; Jill Late Stage Cancer Foundation</td>
<td><a href="http://www.jajf.org">http://www.jajf.org</a></td>
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<tr>
<td>The Oncofertility Consortium</td>
<td><a href="http://oncofertility.northwestern.edu">http://oncofertility.northwestern.edu</a></td>
</tr>
<tr>
<td>Ulman Cancer Fund for Young Adults</td>
<td><a href="http://www.ulmanfund.org">http://www.ulmanfund.org</a></td>
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<tr>
<td>We Believe Foundation</td>
<td><a href="http://www.webelievefoundation.com">http://www.webelievefoundation.com</a></td>
</tr>
<tr>
<td>Young Survival Coalition (for young women diagnosed with breast cancer)</td>
<td><a href="http://www.youngsurvival.org">http://www.youngsurvival.org</a></td>
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</table>
depending on individual malignancies. Nearly 70,000 patients in this age group are diagnosed with cancer each year in the United States, representing more than 7 times more patients than those diagnosed at younger than 15 years of age (Table 1). The spectrum of cancer types that affect the AYA population is unique and different from those that affect the pediatric and older population. Cancer is the leading cause of death among the AYA population, excluding homicide, suicide, or unintentional injury. Lymphomas, melanoma, testicular cancer, female genital tract malignancies, thyroid cancer, bone and soft tissue sarcomas, leukemias, central nervous system (CNS) cancers, breast cancer, and nongonadal germ cell tumors account for 95% of the cancers in this age group. The frequency and incidence of distribution of cancer types is also dramatically different across the age spectrum of the AYA population. See Table 2 for age-specific SEER incidences of cancer by age group and sex in the AYA population.

Quality care for AYA patients with cancer is tied to timely detection, efficient processes for diagnosis, initiation of treatment, promotion of adherence, and access to a multidisciplinary team of health care professionals who are well-versed in the specific issues relevant to this patient population. These issues include fertility, long-term side effects, psychosocial and socioeconomic issues, transportation to clinic appointments, child care, treatment adherence, and the unique biology of disease.

The goal of the NCCN Guidelines for AYA Oncology is to identify issues specific to the AYA population and recommend interventions unique to this patient population; educate physicians regarding the prevalence of cancer in AYAs and its long-term consequences; identify special considerations related to the management of cancer in AYA patients with the aim of improving treatment tolerance, compliance, and clinical outcomes; and promote participation in clinical trials.

**Risk Factors**

With rare exceptions, cancer seems to arise sporadically in most AYAs with a negative family history of cancer. No established risk factors exist for most cancer diagnoses before the age of 30 years. Toxic and environmental exposures that cause cancer in AYAs include chemotherapy and/or radiation therapy (RT) leading to second malignancies in patients treated for cancer during childhood or young adulthood; predisposition to clear cell adenocarcinoma of the vagina or cervix in patients with maternal exposure to diethylstilbestrol; and melanomas induced by ultraviolet light. Infections that predispose AYAs to cancer include cervical carcinoma after exposure to human papillomavirus (HPV), Hodgkin lymphoma (HL), Burkitt lymphoma after Epstein-Barr virus infection, and Kaposi sarcoma and non-Hodgkin’s lymphoma (NHL) in patients with HIV.

Familial cancer syndromes, associated with germline mutations in a variety of genes, affect only a small minority of AYA patients with cancer. However, these syndromes greatly increase the risk for cancer during adolescence and young adulthood in affected patients.

**Breast Cancer**

Young women with germline mutations of BRCA1, BRCA2, TP53 (Li-Fraumeni syndrome), or PTEN (Cowden syndrome), or those who have received mantle field irradiation for HL are at an increased risk of developing breast cancer during young adulthood. Screening for breast cancer may be warranted in AYA patients with inherited or familial risk factors (see the NCCN Clinical Practice Guidelines in Oncology for

<table>
<thead>
<tr>
<th>Age Group (y)</th>
<th>Year</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>15–19</td>
<td>2008</td>
<td>2536</td>
<td>2176</td>
</tr>
<tr>
<td>20–24</td>
<td>2008</td>
<td>3956</td>
<td>3753</td>
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<tr>
<td>25–29</td>
<td>2008</td>
<td>5026</td>
<td>6785</td>
</tr>
<tr>
<td>30–34</td>
<td>2008</td>
<td>6403</td>
<td>10,857</td>
</tr>
<tr>
<td>35–39</td>
<td>2008</td>
<td>9607</td>
<td>18,895</td>
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</tbody>
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*Data for in situ breast cancers are listed separately from Breast Cancers and not included in the “all sites” category.
Colon Cancer

In young adults, hereditary polyposis and nonpolyposis syndromes, inflammatory bowel disease, and radiation exposure are predisposing factors for developing colorectal cancer. \(^1\) Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) is an autosomal dominant syndrome caused by mutations in 1 of the 4 MMR genes (MSH2, MLH1, MSH6, or PMS2), and is associated with colon cancer developing in the AYA population. \(^12\) Familial adenomatous polyposis (FAP) is an autosomal dominant disease caused by germline mutations in the APC gene. This syndrome is associated with thousands of colonic polyps and with the development of colon cancer in most affected patients by 40 years of age. Desmoid tumors are considered to be the most common extracolonic manifestations of FAP, and may be the presenting manifestation of FAP in AYA patients. \(^12\) Screening for colorectal cancers may be warranted in AYA patients with inherited or familial risk factors. See the NCCN Guidelines for Colorectal Cancer Screening (to view the most recent version of these guidelines, visit NCCN.org).

Sarcomas

AYA patients with Li-Fraumeni syndrome or germline mutations in the retinoblastoma (RB) gene are at a higher risk of developing osteosarcoma. AYA individuals with germline mutations in the RB gene have often been treated for RB during early childhood. \(^13\) AYAs with a family history of Li-Fraumeni syndrome have a higher risk of developing not only sarcomas but also a wide variety of malignancies, including leukemia, brain tumors, breast cancer, and adrenocortical carcinoma before 40 years of age. \(^14\) Patients with succinate dehydrogenase (SDH) gene mutations are at risk for paraganglioma and pheochromocytoma, gastrointestinal stromal tumors (GISTs), renal cell carcinoma, and papillary thyroid carcinoma during adolescence and young adulthood. Testing for germline mutations in the SDH subunit should be considered for AYA patients with wild-type GISTs lacking KIT or PDGFRα mutations. \(^15,16\) Patients with germline mutations in neurofibromatosis type 1 (NF1) carry a

Table 2  Age-Specific SEER Incidences\(^a\) of Cancer by Age Group and Sex in the Adolescent and Young Adult Population (2004–2008)\(^b\)

<table>
<thead>
<tr>
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<td></td>
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<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
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<tr>
<td>Bone sarcomas</td>
<td>2.1</td>
<td>1.3</td>
<td>1.2</td>
<td>0.9</td>
<td>0.7</td>
<td>0.7</td>
<td>0.6</td>
<td>0.6</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Carcinoma of breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–</td>
<td></td>
<td>1.4</td>
<td></td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Central nervous system cancers</td>
<td>2.2</td>
<td>2.1</td>
<td>2.2</td>
<td>2.3</td>
<td>3.1</td>
<td>2.2</td>
<td>3.6</td>
<td>2.6</td>
<td>4.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Carcinoma of cervix and uterus</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
<td>6.3</td>
<td></td>
<td>14.3</td>
<td></td>
<td>20.9</td>
<td></td>
</tr>
<tr>
<td>Carcinoma of colon and rectum</td>
<td>0.3</td>
<td>0.3</td>
<td>0.9</td>
<td>1.0</td>
<td>2.1</td>
<td>1.9</td>
<td>4.4</td>
<td>4.5</td>
<td>9.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Carcinoma of respiratory tract</td>
<td>0.3</td>
<td></td>
<td>0.3</td>
<td></td>
<td>0.5</td>
<td>0.6</td>
<td>1.1</td>
<td>1.3</td>
<td>2.8</td>
<td>3.1</td>
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<tr>
<td>Germ cell neoplasms</td>
<td>4.3</td>
<td>1.1</td>
<td>10.6</td>
<td>1.2</td>
<td>14.0</td>
<td>1.1</td>
<td>13.4</td>
<td>0.9</td>
<td>11.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Leukemias</td>
<td>3.7</td>
<td>2.6</td>
<td>3.0</td>
<td>2.3</td>
<td>3.0</td>
<td>2.2</td>
<td>3.4</td>
<td>2.8</td>
<td>4.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>3.0</td>
<td>3.1</td>
<td>4.3</td>
<td>4.7</td>
<td>4.0</td>
<td>4.5</td>
<td>4.0</td>
<td>3.8</td>
<td>3.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>2.1</td>
<td>1.5</td>
<td>2.9</td>
<td>1.9</td>
<td>3.8</td>
<td>2.8</td>
<td>5.5</td>
<td>4.0</td>
<td>8.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.2</td>
<td>1.9</td>
<td>2.5</td>
<td>6.0</td>
<td>4.7</td>
<td>9.9</td>
<td>7.4</td>
<td>12.3</td>
<td>10.9</td>
<td>16.5</td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td>1.4</td>
<td>1.5</td>
<td>2.0</td>
<td>1.7</td>
<td>3.1</td>
<td>2.1</td>
<td>4.2</td>
<td>2.8</td>
<td>5.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>0.7</td>
<td>3.4</td>
<td>1.3</td>
<td>8.8</td>
<td>2.7</td>
<td>14.2</td>
<td>4.0</td>
<td>20.2</td>
<td>5.3</td>
<td>24.6</td>
</tr>
</tbody>
</table>

\(^a\)Rates are per 100,000.
10% lifetime risk for malignant peripheral nerve sheath tumors, and an increased risk for other malignancies, including GISTs and early breast cancer in women.\textsuperscript{17}

**Screening**

Cancer screening in some circumstances, particularly in cervical, breast, and colorectal cancers, can significantly reduce mortality if directed at the appropriate age group and if the results are interpreted and followed up appropriately.\textsuperscript{18} However, no age-specific screening tests have been developed that would increase early detection in AYAs with cancer, and in some instances screening tests have been associated with false-positive results leading to false diagnosis and unnecessary treatments.\textsuperscript{19} Therefore, simple and accurate tests and potential risks and benefits are important to identify before they are implemented in AYA patients. AYAs with cancer should be made aware of the importance of early diagnosis and self-examination of the skin, breast (for women), and testicles (for men) as recommended by the American Cancer Society. They should also be educated regarding the benefits of early detection and treatment.\textsuperscript{5}

**Diagnosis**

The onset of new symptoms in AYAs may not immediately trigger evaluation for malignancy, because of the relatively low incidence of cancer in this age group and the resulting low index of suspicion on the part of patients and primary care providers. AYAs are at a higher risk of delayed cancer diagnosis, which may result in a more advanced stage of cancer that requires more therapy and is associated with a worse prognosis.\textsuperscript{5} Some studies have reported that adolescents experience longer lag times (interval between symptom onset and diagnosis) than children.\textsuperscript{20–22} Lack of health insurance, inexperienced physicians, and workup that is inappropriate for the patient’s age are some causes of delayed diagnosis in AYAs with cancer. In a retrospective analysis of 503 patients aged 15 to 29 years with previously untreated cancer, the advanced stage of cancer at diagnosis and lack of health insurance were significantly associated with longer lag times.\textsuperscript{23} Those with public or no health insurance had longer lag times than those with private health insurance in most of the cancers evaluated. Patients with leukemia and NHL had shorter lag times (2–5 weeks) than those with sarcomas and thyroid cancer (20–24 weeks), irrespective of the insurance type. In addition to health insurance, education and employment status are also likely to influence lag time, although these factors were not evaluated in this study.

**Special Considerations in the Management of AYAs With Cancer**

All AYA patients should undergo comprehensive assessment after the diagnosis of cancer, which should include psychosocial assessment, discussion of infertility risks associated with treatment and options for fertility preservation, and genetic and familial risk assessment (within 2 months after the start of therapy).

**Age-Appropriate Care: Pediatric Versus Adult Cancer Centers**

AYA patients with cancer can be treated at either pediatric or adult cancer centers.\textsuperscript{24} Retrospective analyses have shown that AYA patients with certain pediatric-type cancers, such as acute lymphoblastic leukemia (ALL),\textsuperscript{25–29} rhabdomyosarcoma,\textsuperscript{30} and Ewing sarcoma,\textsuperscript{31} have superior outcomes when treated with pediatric protocols. Alternatively, there is a lack of compelling evidence that pediatric protocols improve outcomes in AYA patients with acute myeloid leukemia (AML), HL, and NHL.\textsuperscript{32–34} 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.\textsuperscript{1–3} Care should be provided at medical centers with broad access to clinical trials (standard-of-care registry trials and trials evaluating novel therapies).\textsuperscript{24} Pediatric cancer centers enroll more adolescents into clinical trials (35% vs. 12% at nonpediatric 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%).\textsuperscript{35–37} More recently, Parsons et al\textsuperscript{38} reported that AYA patients who are treated by nonpediatric 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.\textsuperscript{39,40}
The treatment and appropriate location of care vary with the type of cancer and the availability of family, community, and institutional supports. 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, and medical subspecialty services appropriate to the cancer diagnosis, such as orthopedic surgeons with experience in limb-sparing surgery for patients with extremity sarcomas. Centers should adopt the appropriate evidence-based approach, which includes adult centers implementing treatment based on pediatric protocols that have shown superior outcomes in AYA patients and pediatric centers adopting adult regimens that have shown benefit in this patient population.

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.

**Treatment Options**

AYA patients can usually tolerate more intensive therapies than older adults, because they have fewer comorbid conditions that limit the intensity of treatment in older adults. Dose-intensive and dose-dense treatment is associated with improved outcomes. Every AYA patient with cancer should be treated with aggressive therapy if they have no contraindications.

Treatment-related issues in AYA patients with cancer may differ from those in pediatric or older adults because of the distinct biology of the disease. 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 AYAs. AYA patients have fewer comorbid conditions compared with older cancer patients, and thus are usually able to tolerate intense chemotherapy and surgery with less morbidity. Appropriate management of symptoms and side effects to reduce the severity and toxicity of treatment should be an integral part of the management of AYAs with cancer.

Surgery, RT, chemotherapy, and hematopoietic stem cell transplantation (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. Surgery: Surgery is more feasible in AYAs with cancer because they have fewer comorbidities than older patients, and anesthesia is easier to administer than in children. At the same time, 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. The extent of surgery is dependent on the type and location of cancer. In some cases, extensive surgery requiring removal of part or all of an organ or limb may be necessary. With the recent advances in surgical techniques and chemotherapy, limb-sparing surgery is now feasible for most patients with extremity sarcoma and osteosarcoma.

**RT:** RT has been associated with an increased risk for late mortality; development of second malignancies; pulmonary, cardiac, and thyroid dysfunction; and chronic health conditions and growth abnormalities. AYAs with cancer receiving RT to the testes or ovaries are at risk of developing infertility later in life. Women who receive chest radiation for HL between 10 and 30 years of age are at increased risk of developing breast cancer. 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. See also “Impact of Treatment on Fertility and Fertility Preservation” and “Late Effects in AYA Cancer Survivors,” pages 1133 and 1139, respectively. Adolescents are more vulnerable to radiation-induced spinal cord dysfunction, presumably because of elongation of the cord during the growth spurt.

**Chemotherapy:** Alkylating agent-based chemotherapy is associated with a higher risk of infertility in both male and female patients. See “Impact of Treatment on Fertility and Fertility Preservation,” page 1133. Anthracycline-based chemotherapy is associated with cardiac dysfunction, whereas neu-
rotoxic chemotherapies, such as methotrexate and cytarabine, can result in CNS dysfunction. Higher cumulative doses of cisplatin, ifosfamide, or epipodophyllotoxin are associated with hearing loss, renal dysfunction, and secondary AML, respectively. See also “Late Effects in AYA Cancer Survivors,” page 1139.

Pain, fatigue, nausea, vomiting, mucositis, hair loss, infection, and myelosuppression are some of the acute side effects of chemotherapy. Reversible toxicities (as mentioned earlier) do not necessarily warrant dose reductions. See the NCCN Guidelines for Supportive Care for the management of treatment-related toxicities (available at NCCN.org). 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 intensive screening is essential for patients receiving chemotherapy regimens associated with irreversible organ damage.

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. Younger patients (age < 50 years) may be more susceptible to ANV, because they generally receive more aggressive chemotherapy and have poorer emesis control than older patients. Behavioral therapy has been used in patients with ANV. See the NCCN Guidelines for Antiemesis (available at NCCN.org).

**HSCT:** HSCT is a potentially curative therapeutic option for an increasing number of AYA patients with leukemias and lymphomas. Gonadal dysfunction related to high-dose conditioning chemotherapy and RT, graft-versus-host disease, and chronic immunosuppression are the major posttransplant complications associated with HSCT in men and women. Survivors are also at increased risk for late complications of treatment, including recurrent infections, secondary cancers, cardiac dysfunction, growth failure, neurocognitive delay, and other end-organ dysfunction. HSCT survivors are at an increased risk of developing severe or life-threatening chronic health conditions, endocrine complications, or secondary neoplasms compared with noncancer populations and patients with cancer treated conventionally. Allogeneic transplant survivors irradiated at 30 years or younger are at higher risk of developing secondary solid cancers. These findings highlight the increasingly recognized need for long-term follow-up care that incorporates screening and surveillance of AYA survivors of HSCT. See “Late Effects in AYA Cancer Survivors,” page 1139.

### Impact of Treatment on Fertility and Fertility Preservation

Although fertility preservation of fertility is an issue of crucial importance in AYA patients, it is currently one of the most underprescribed and least implemented services in AYA patients with cancer. The 2006 ASCO guidelines recommend that providers discuss the options for fertility preservation with all new patients diagnosed with cancer.

Infertility is a major consequence of cancer therapy in both men and women. The impact of cancer therapy on fertility is related to the age of the patient at treatment and is dependent on the duration, dose-intensity, and type of treatment. Alkylating agent–based chemotherapy is more harmful to the ovaries and testis than regimens containing nonalkylating agents. High doses of cranial RT can impair hypothalamic pituitary function, resulting in the deficiency of gonadotropin-releasing hormone (GnRH) and impairment in fertility in both men and women. Gonadal exposure to low doses of radiation can cause oligospermia or azoospermia in men. Higher doses of radiation are associated with both ovarian and uterine dysfunction in women. **NCCN Recommendations for Fertility Preservation:** Available evidence strongly supports that fertility preservation is of great importance in AYA patients with cancer and should be an essential part in the management of their cancer. Women are at risk for premature ovarian failure due to chemotherapy and men are at risk for azoospermia after therapy, which may or may not resolve over time. Fertile Hope developed a risk calculator based on a compilation of clinical experience and published research on common cancer treatments that may im-
Fertility Preservation for Women: Much of the data on the impact of cancer on fertility are from the Childhood Cancer Survivor Study (CCSS) in patients younger than 21 years at diagnosis. Hypothalamic or pituitary radiation, pelvic RT, and/or increasing alkylating agent doses have been associated with acute ovarian failure and premature menopause. Total body irradiation (TBI) and abdominal and pelvic RT have been shown to cause uterine dysfunction. Gonadal failure has also been reported in women diagnosed with cancer in their adolescence and young adulthood. The incidence of gonadal failure is dependent on age at diagnosis and the cumulative dose of alkylating agents.

Fertility is a major concern for young women receiving chemotherapy for breast cancer and HL. Among young women treated with adjuvant chemotherapy for breast cancer, the risk for chemotherapy-related amenorrhea and premature menopause is significantly higher for those with newly diagnosed breast cancer treated with chemotherapy who are older than 35 years. In a cohort study of 518 female survivors of HL diagnosed between 14 and 40 years of age, those who were older (22–39 years of age) at first treatment had a higher risk for developing premature menopause after treatment compared with younger patients (14–21 years). Similarly, the risk of developing premature ovarian failure is also higher among young women receiving chemotherapy and RT for HL, irrespective of their age at treatment (38% for those diagnosed between 30 and 40 years of age; 37% for those diagnosed between 9 and 29 years of age).

Oophoropexy and embryo cryopreservation after in vitro fertilization (IVF) are the 2 established options for fertility preservation in women. Oophoropexy involves surgically displacing the ovaries out of the planned radiation field to minimize ovarian damage and has been shown to preserve ovarian function. It should be considered for all female patients who will be receiving RT and may be performed either during cancer surgery or in a separate surgical procedure.

If cancer therapy can be delayed long enough for a cycle of oocyte stimulation (especially for patients with low- and intermediate-risk HL and low-grade sarcomas), the possibility of embryo cryopreservation should be discussed. Embryo cryopreservation after IVF has been highly successful in women younger than 40 years. However, this method requires a male partner or sperm donor.

Mature oocyte cryopreservation and ovarian tissue grafting and freezing are emerging techniques for fertility preservation in young women. They are still considered investigational and their efficacy is unclear. These options are available in some areas, most frequently in the context of clinical trials. Mature oocyte cryopreservation is a potential alternative for single women but, like embryo cryopreservation, requires hormone stimulation. Ovarian tissue grafting does not require hormonal stimulation, and therefore no long delay in treatment is necessary. However, this procedure would not be considered appropriate for some women (eg, those with a malignancy in whom reimplantation of malignant cells could occur with grafting).

GnRH agonists have been used as ovarian protectors during chemotherapy. Although some investigators have reported that GnRH agonist administration before and during combination chemotherapy may preserve posttreatment ovarian function in women with breast cancer younger than 40 years, others have observed no protection of the ovarian reserve in young women with advanced-stage HL treated with GnRH and escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) chemotherapy. A more recent systematic review and meta-analysis suggests that although GnRH with chemotherapy in premenopausal women is associated with higher rates of spontaneous resumption of menses and ovulation, it is not associated with improvement in pregnancy rates. Additional studies are required to confirm these findings. Menstrual suppression does not protect the ovaries. Medroxyprogesterone or oral contraceptives may be used in protocols that are predicted to cause prolonged thrombocytopenia, and thus present a risk for menorrhagia.
Management of Cancer During Pregnancy: The diagnosis of cancer during pregnancy can be extremely difficult for the patient, family, and physician. The most common cancers diagnosed during pregnancy are breast, cervical, ovarian, and thyroid cancers; leukemia; lymphoma; and melanoma.25 Given the rarity of this clinical situation, limited data are available on the management of cancer during pregnancy.26,27 AYA women diagnosed with cancer during pregnancy require individualized treatment from a multidisciplinary team, including medical, surgical, and radiation oncologists; an obstetrician; a pathologist; and a radiologist. Potential benefits and risks of chemotherapy and RT for both the mother and the fetus must be carefully evaluated before the start of treatment. See the NCCN Guidelines for Breast Cancer for the management of women with breast cancer during pregnancy (available at NCCN.org). Referral to a gynecologic oncologist and perinatologist with expertise and knowledge of the physiological changes that occur during pregnancy is strongly recommended.

Fertility Preservation for Men: In men who undergo either chemotherapy or RT, germ cell dysfunction is more common than treatment-induced Leydig cell dysfunction.79 Leydig cell dysfunction occurs at RT doses higher than those associated with germ cell dysfunction. AYA men treated with a testicular radiation dose of 20 Gy or more are at high risk for Leydig cell dysfunction, whereas testicular radiation doses of 2 Gy or more can impair spermatogenesis resulting in permanent azoospermia.79 TBI used as part of high-dose conditioning therapy before HSCT can also affect the testis, resulting in permanent infertility in most AYA men undergoing this treatment.80 Among patients treated with alkylating agent–based chemotherapy, cumulative doses of cyclophosphamide (≥ 20 g/m²) or ifosfamide (> 60 g/m²) are associated with a high probability of oligospermia, azoospermia, and infertility, whereas many individuals treated with a cumulative dose of 7.5 to 10 g/m² or less retain normal sperm production.80

Semen cryopreservation and transplantation of spermatogonia are the options for fertility preservation in male patients.86,57 Semen cryopreservation before the start of treatment is the most reliable and well-established means of preserving fertility in AYA men with cancer. Sperm banking should be offered for all patients at diagnosis. AYAs can use either the local sperm bank or the unique collection and preservation kit that is available through Live:On kit (www.liveonkit.com). Because the age and comfort level of the patients must be taken into account when discussing sperm banking, 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. The success of sperm banking may be limited by the fact that some men with newly diagnosed cancer, such as those with HL, may already have azoospermia associated with the disease.

Limited evidence is available regarding the efficacy of hormone suppression in reducing the risk of infertility during chemotherapy.31 Cryopreservation and subsequent transplantation of spermatogonial stem cells are still experimental and may be an ultimate alternative for some patients in whom semen cryopreservation is not possible.

Psychosocial Issues

AYA individuals diagnosed with and treated for cancer have psychosocial issues that are distinct from those of pediatric and adult patients.82,83 Some of the challenges for 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.84 AYA individuals undergo developmental stages marked by rapid changes in cognitive and emotional growth, and these issues must be considered so that developmentally appropriate psychosocial and supportive care can be delivered to this population.85 Psychosocial needs for AYAs with cancer should be assessed across the following domains: 1) individual function (developmental, emotional, and behavioral issues); 2) relationships (family, peer, and health care professional); 3) socioeconomic issues; and 4) supportive care services/interventions.

Individual Function

Developmental Issues: AYAs with cancer have to 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; and independently making decisions about their future that involve
education, career, or employment. 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 because of treatment will have negative consequences for their long-term career opportunities, financial status, and lifetime earnings.

During the treatment period, AYAs 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.

**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 matured cognitive and emotional coping abilities. Recent studies suggest that the rates of psychological distress are significantly greater among AYAs compared with older adults. Kazak et al recently 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.

**Behavioral Issues:** AYA patients with cancer may also engage in risky behaviors (tobacco, alcohol, or substance abuse) that may impair their health. Older age at cancer diagnosis, lower household income, less education, no pulmonary-related cancer treatment, and no brain radiation were independently associated with a statistically significant relative risk of smoking initiation. 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. Low perception of susceptibility to late effects, older adolescence compared with early adolescence, and worry were the strongest predictors of substance abuse.

Although AYA patients may be aware of the complications associated with tobacco, alcohol, or substance 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 must be aware of this and address the issues in a sensitive and confidential manner.

**NCCN Recommendations for Supportive Care Services/Interventions:**

- For all AYA patients, provide counseling regarding the risks of treatment-related infertility and discuss options for fertility preservation before the start of therapy.
- Provide AYA patients with flexible treatment dates, consultation times, and procedures to enable them to continue with their treatment without interrupting their school/work or other normal activities.
- 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.
- Because the incidence of sexually transmitted infections peaks among AYAs aged 15 to 24 years, provide preventative health education about sexually transmitted diseases.
- Recommend HPV immunization (if not previously administered) for the prevention of secondary cancers, because the vaccine has been shown to prevent cervical carcinoma and anal epithelial neoplasia, the precursor to carcinoma.
- Prescribe and provide nutrition and exercise recommendations for all AYAs.
- 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).

**Adherence to Treatment**

Adherence is defined as the extent to which a person’s behavior corresponds with agreed recommendations from a health care provider. Nonadherence to recommended treatment and follow-up care contribute to poor clinical outcomes in AYAs with cancer.
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.\textsuperscript{99} 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.\textsuperscript{99,100}

Nonadherence to other components of cancer treatment (eg, failure to keep appointments for treatment or follow-up, refusing medical examinations, not preparing for procedures or therapy) was also identified in AYA patients. Treatment nonadherence in clinical trials can 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 with cancer include emotional functioning (depression and 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.\textsuperscript{101} In a randomized controlled trial, video game intervention significantly improved treatment adherence to prophylactic antibiotics among adolescents and young adults with acute leukemia, lymphoma, and soft tissue sarcoma.\textsuperscript{102} A recent meta-analysis showed that behavioral and multicomponent interventions have been shown to have a moderate effect on improving treatment adherence in children (aged 2–15 years) with chronic conditions such as diabetes, asthma, and cystic fibrosis.\textsuperscript{103}

Additional studies are needed evaluating the effect of interventions on improving adherence in AYA patients with cancer. In the absence of data on this effect, the findings from the studies involving AYA patients with other chronic diseases could be extrapolated to this patient population.

**NCCN Recommendations to Promote Adherence:**

- Provide education and/or guidance about each medication before the start of treatment and every time a change in treatment occurs. Review the list of medications and their dose, purpose, and adverse effects.\textsuperscript{99,100}
- 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’s lifestyle and normal activities.\textsuperscript{99,100}
- Provide access to systematic and standardized symptom management for side effects related to cancer treatment.\textsuperscript{99,100} See the NCCN Guidelines for Supportive Care (available at NCCN.org).

**Relationships**

**Social, Peer, and Family Relationships:** AYAs often must endure lengthy hospital stays under the supervision of health care providers, resulting in significant isolation from their family members and peer group.\textsuperscript{88} Isolation and alienation are common among AYA individuals diagnosed with cancer, because they often miss out on the life experiences shared by their nonill peers. Reinforcing relationships with family, peers, and health professionals is an important aspect of life for AYAs with cancer.\textsuperscript{85,104}

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 and other AYA cancer survivors) in helping AYAs cope with cancer and overcome feelings of loneliness.\textsuperscript{82,85} In one study, AYAs with cancer (aged 16–22 years) identified social support (friends and health care providers) as their major coping strategy to deal with cancer, whereas family support was identified as their important source for emotional support.\textsuperscript{105} In another study, 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.\textsuperscript{97}

Peer support programs assist AYA patients and survivors in establishing and maintaining relationships with their normal peers and with other AYAs with cancer; offer opportunities to achieve age-related developmental tasks (building interpersonal and problem-solving skills); and promote positive
Communicating information to AYAs can be challenging, especially because the AYA population has several subgroups with different levels of cognitive and emotional development. Establishing direct communication with patients on an individual basis is very important, with sufficient sensitivity to each patient’s needs and preferences. 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 an age-appropriate manner, allowing them time to process the information, and the information should be delivered in a caring manner. AYAs prefer that information about their cancer and cancer-related risks be communicated to them in a manner that is positive, respectful, and nonjudgmental. 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. Because evidence shows that AYA patients are willing to use the Internet to get health information and support, providing them with a list of recommended and reliable age-appropriate online sources to access information about their cancer would be helpful, particularly with regard to treatment and late effects, fertility preservation, mental health counseling, peer support groups, diet, and nutrition. See Online Resources for AYA Patients and Survivors on page 1128.

**NCCN Recommendations for Supportive Care Services/Interventions:**

- Promote communication between AYA patients and family members (parents, spouse/partners, and siblings).
- Provide information to family members and partners about psychosocial support and behavioral services to increase awareness of the possible psychosocial issues associated with a diagnosis of cancer in AYAs.
- Consider family-based intervention models from pediatrics (eg, parent support groups, Impact of Traumatic Stressors Interview Schedule).
- Establish direct communication with individual patients, providing age-appropriate information about their cancer, treatment options, and potential side effects, thus reinforcing the importance of AYA involvement in decision-making.
- 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.
- Provide information about peer support groups and create flexible visiting hours and an environment that will encourage peers to visit AYA patients.

**Socioeconomic Issues**

AYAs are much more likely than adults or children to be uninsured or underinsured, with many of them in a transition between their parents’ insurance and their independent insurance. 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. Furthermore, unemployment and lack of health insurance seem to be significant predictors of psychological distress in the childhood cancer survivor population. Uninsured AYA patients are also less likely to participate in clinical trials. Advanced stage of cancer at diagnosis and lack...
of health insurance were significantly associated with longer time to cancer diagnosis in AYAs.\textsuperscript{23} 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.\textsuperscript{84} AYA patients with employment also experience problems in obtaining health and life insurance because of their preexisting cancer history.\textsuperscript{82} 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, childcare, and non–treatment-related costs.\textsuperscript{82} Financially independent AYA patients 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:**

- Assess AYA patients’ health insurance status and potential, and provide information on potential sources of coverage (eg, Medicaid, Social Security, and disability 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, food stamps).
- 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.
- For those who desire to receive complementary and alternative medicine, refer them to reputable providers of these services.
- Provide information about reliable online sources to access age-appropriate information related to their cancer. See Online Resources for AYA Patients and Survivors on page 1128.
- Educate AYA patients with cancer about their long-term follow-up care for monitoring and treatment of late effects, long after completion of treatment.
- Integrate financial assistance for AYA cancer survivors into their survivorship plans.

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**Survivorship Issues**

**Late Effects in AYA Cancer Survivors**

AYA cancer survivors are at increased risk for late effects related to cancer treatment, and the risk for long-term effects is dependent on the age at initial diagnosis and the type of treatment.\textsuperscript{115–117} In addition, the risk for many late effects may also be influenced by family history, lifestyle behaviors, and comorbid health conditions. Much of the understanding of the long-term outcomes of AYA cancer survivors comes from the CCSS, which includes long-term survivors of childhood and adolescent cancers that were diagnosed before 21 years of age.\textsuperscript{118,119} No large cohort studies have addressed the survivorship issues related to cancer diagnosed in young adult patients between the ages of 22 and 39 years. Among adult survivors of childhood and adolescent cancer, Oeffinger et al\textsuperscript{118} reported that by 30 years after the cancer diagnosis, the cumulative incidence of a chronic health condition was 73%, with a cumulative incidence of 42% for severe, disabling, or life-threatening conditions or death. Importantly, the risk for a chronic health condition (ie, long-term or late effect) was similar for those diagnosed with the primary cancer in adolescence and in childhood. Age at treatment exposure modifies the risk of some late effects (eg, breast cancer after chest radiation, cardiomyopathy after anthracycline chemotherapy) but not others (eg, ischemic coronary artery disease after chest radiation).\textsuperscript{120,121}

Although several single cancer studies have assessed long-term outcomes among HL and testicular cancer survivors across the AYA age range, the long-term outcomes of survivors of other cancers occurring in young adulthood, such as breast, ovarian, and thyroid cancers and melanoma, remain understudied. Outcomes from the CCSS among those diagnosed between the ages of 15 and 20 years are particularly relevant for these guidelines. Because of the paucity of literature on survivorship issues related to cancer diagnosed during adolescence and young adulthood, the findings from the CCSS and similar studies focusing on childhood and adolescent cancer survivors could be extrapolated to the survivors of AYA cancers, albeit with caution.

Some of the more common late effects among AYA cancer survivors are discussed in the following sections.
**Secondary Cancers:** AYA cancer survivors are at significant risk of developing a variety of secondary cancers compared with the general population. The risk and specific types of secondary cancers are widely dependent on the type of initial cancer diagnosis and treatment exposure. Older age at diagnosis (15–21 years) was associated with increased risk for breast cancer, nonmelanoma skin cancers, and other solid organ cancers (including head and neck, small intestine, and colorectal cancers).

AYA survivors of HL diagnosed between 21 and 39 years of age are at increased risk of developing secondary cancers. The most frequently observed secondary cancers are breast, lung, thyroid, and gastrointestinal cancers. Adolescent or young women treated with chest radiation for HL are at significantly increased risk of developing secondary breast cancer, and the risk for secondary breast cancer among HL survivors is strongly associated with age at diagnosis and mediastinal radiation dose. In a cohort of 770 female survivors who had been diagnosed with HL before 41 years of age, the risk of developing breast cancer increased with increasing radiation dose (≥ 38.5 Gy). In an international, population-based study of 3817 female survivors of HL diagnosed at 30 years of age or younger, Travis et al reported that for women treated at age 25 years with a chest radiation dose of at least 40 Gy without alkylating agents, the estimated cumulative absolute risks of developing breast cancer by age 35, 45, and 55 years were 1.4%, 11.1%, and 29.0%, respectively.

Alkylating agent–based chemotherapy for HL has been associated with a modestly increased risk for secondary lung cancers in patients diagnosed at 40 years or younger, and the risk increased with both increasing number of cycles of alkylating agents and the cumulative dose. In this study, the risk of secondary lung cancer was substantially higher among survivors who smoked (9.6% due to treatment alone compared with 63.3% due to the combination of treatment and smoking). In a recent collaborative British Cohort study that assessed the risk of developing secondary cancers in 5798 patients diagnosed with HL between 15 and 34 years of age, the 20-year cumulative risk of second cancer was 13% and 18% for chemotherapy alone and combined modality therapy, respectively. Risks for secondary lung cancer, NHL, and leukemia were significantly higher after treatment with chemotherapy alone, whereas combined modality therapy was associated with a higher risk for these and several other cancers.

AYA survivors of testicular cancer are also at significantly increased risk of developing secondary cancers, including contralateral testicular cancer, leukemia, malignant mesothelioma, and cancers of the lung, colon, esophagus, stomach, and pancreas. In a population-based study of 29,515 testicular cancer survivors, the 15-year cumulative risk of developing contralateral testicular cancer was almost 2%, which is 12-fold higher than that of the general population.

In an international, population-based study of 40,576 testicular cancer survivors, the cumulative risk of developing solid tumors by 75 years of age was slightly higher for seminoma patients than for nonseminoma patients diagnosed at 35 years of age (36% and 31%, respectively). The combination of chemotherapy and RT was associated with a larger risk of secondary solid tumors than RT alone, although the difference was not statistically significant. Secondary leukemia related to chemotherapy with topoisomerase II inhibitors and alkylating agents has also been reported in testicular cancer survivors. In one study, the cumulative incidence of secondary AML was 0.5% at 2 years after treatment with high-dose chemotherapy (with a median cumulative etoposide dose of 4.9 g/m²) and autologous stem cell transplantation. In another study involving 42,722 one-year survivors of testicular cancer, the estimated excess cumulative leukemia risk was 0.23% at 30 years after testicular cancer diagnosis. The risk for secondary AML was higher for patients treated with chemotherapy compared with those treated with RT alone.

The risk for secondary malignancies among survivors of cervical and breast cancers, NHL, and melanoma has been assessed in only a few cohort studies. Among 104,760 one-year survivors of cervical cancer, patients heavily treated with RT were at increased risk for second cancers at sites in proximity to the cervix beyond 40 years of follow-up. The 40-year cumulative risk for any second cancer was higher among women diagnosed before 50 years of age than among those diagnosed after 50 years of age (22.2% and 16.4%, respectively). In a population-based cohort of 376,825 one-year survivors of breast cancer from the Scandinavian cancer registries, women diagnosed at 40 years or
younger with localized disease were particularly at risk of developing a second cancer at 30 or more years after breast cancer diagnosis.\textsuperscript{140} In an analysis of 28,131 patients from the Swedish Cancer Registry, the risk of developing subsequent solid tumors after NHL during the first decade was higher among patients diagnosed between 20 and 39 years of age compared with those who were 40 years of age or older at diagnosis.\textsuperscript{141} In the SEER database analysis of 89,515 melanoma survivors, patients diagnosed at younger than 30 years had the highest risk of developing secondary cancers (breast, prostate, and NHL being the most common cancers) at more than 20 years after initial diagnosis.

Long-term AYA survivors of pediatric-predominant cancers, including ALL, CNS tumors, and bone and soft tissue sarcomas, are also at risk of developing secondary cancers. The risk is especially higher among patients diagnosed at a younger age (≤ 17 years for ALL and CNS tumors; ≤ 18 years for bone and soft tissue sarcomas).\textsuperscript{122} Among long-term survivors of bone cancers at 25 years after diagnosis, the cumulative incidence of subsequent cancers is higher for those diagnosed with Ewing sarcoma than for those diagnosed with osteosarcoma (9.0% and 5.4%, respectively).\textsuperscript{142,143}

Clinicians who provide care for most AYA cancer survivors must implement and evaluate methods for improving awareness of secondary cancers. They must also implement appropriate surveillance strategies for early detection of these malignancies.\textsuperscript{144} An annual breast MRI and mammogram are recommended for women treated with a chest radiation dose of 20 Gy or more before 30 years of age. A colonoscopy is recommended starting at age 35, or 10 years after radiation, whichever occurs last, for patients treated with abdominal or pelvic radiation of 30 Gy or more.

**Cardiovascular Complications:** Cardiovascular complications (congestive heart failure [CHF], myocardial infarction [MI], pericardial disease, and valvular abnormalities) are the leading nonmalignant cause of death among survivors of AYA cancers.\textsuperscript{145} Mediastinal irradiation and anthracycline-based chemotherapy are the strongest risk factors for late cardiovascular complications in AYA survivors of HL.\textsuperscript{121,146,147} In the British Cohort study of 7033 patients with HL, the risk of death from MI was highest for patients younger than 35 years at the time of treatment with supradiaphragmatic RT.\textsuperscript{147} Patients treated with anthracyclines were at increased risk for MI within 1 year after the first treatment, whereas the risk for MI among patients treated with supradiaphragmatic RT and vincristine without anthracyclines increased sharply after the first year of follow-up.\textsuperscript{147} In another study of 1474 survivors of HL younger than 41 years at the time of treatment, mediastinal RT increased the risk of MI, CHF, and valvular disorders, whereas the addition of anthracyclines to RT elevated the risks of CHF and valvular disorders.\textsuperscript{121} The 25-year cumulative incidence of CHF after mediastinal RT and anthracyclines was 8%.

Cisplatin-based chemotherapy is associated with a long-term risk for cardiovascular complications in testicular cancer survivors.\textsuperscript{148-150} In a Dutch study of 2512 testicular cancer survivors, those with nonseminoma testicular cancer younger than 30 years at diagnosis treated with mediastinal irradiation and chemotherapy with cisplatin, vinblastine, and bleomycin were at increased risk for MI within 20 years of treatment.\textsuperscript{148} More recently, Haugnes et al.\textsuperscript{149} reported that treatment with cisplatin, bleomycin, and etoposide and/or RT was associated with increased risks for cardiovascular disease in testicular cancer survivors; chemotherapy alone or in combination with RT significantly increased the risk for MI.

Survivors of brain tumors, leukemia, NHL, and bone and soft tissue sarcomas treated with anthracyclines and cardiac irradiation are also at significantly higher risk of adverse cardiovascular complications. However, most patients included in these studies were younger than 21 years at diagnosis.\textsuperscript{151}**Pulmonary Complications:** Chemotherapy and chest radiation are associated with pulmonary toxicity and can compromise pulmonary function in survivors of AYA cancer.\textsuperscript{150,152} Age at diagnosis (15–21 years compared with < 15 years) and pulmonary toxic chemotherapy alone or combined with chest radiation were associated with a significantly increased relative risk of lung fibrosis and pleurisy.\textsuperscript{152} The cumulative incidence increased up to 15 to 20 years after diagnosis. Other complications include recurrent pneumonia, chronic cough, supplemental oxygen use, and shortness of breath.

A large international study reported a significant increase in mortality from respiratory diseases among testicular cancer survivors treated with chemotherapy compared with the general
population. Risk factors for pulmonary toxicity include age at diagnosis, cumulative bleomycin dose, reduced glomerular filtration rate, renal dysfunction, and stage IV disease at presentation. Recently, Haugnes et al. reported that among 1049 testicular cancer survivors, those treated with large cumulative cisplatin doses or chemotherapy combined with pulmonary surgery had significantly reduced pulmonary function compared with those treated with surgery alone. Bleomycin dose was not associated with restrictive lung disease. Instead, in a multivariate model, cisplatin dose (P = .007) and age at diagnosis (P = .008) were associated with the risk for restrictive lung disease.

Neurologic Complications: AYA survivors of brain tumors treated with cranial RT are at increased risk for neurologic complications, including hearing impairments, cataracts and other vision problems, seizure disorders, and coordination and motor control problems. However, these findings are relevant to survivors diagnosed at 21 years of age or younger.

Long-term AYA survivors of testicular cancer who were treated with cisplatin-based chemotherapy are at risk for neurologic complications, such as sensory neuropathy, tinnitus, hearing impairment, and Raynaud phenomenon (white or cold hands or feet on cold exposure). Among 1814 survivors of testicular cancer included in a Norwegian observational study, Raynaud-like phenomena were the most frequently reported complications (39% of men), followed by paresthesia of the hands or feet (29%) and tinnitus and hearing impairment (22% and 21%, respectively) in men treated with chemotherapy compared with those not treated with chemotherapy. The incidences of paresthesia of the feet were also higher among men treated with RT.

Stroke, although relatively uncommon, is a devastating neurologic complication in AYA survivors of brain tumors and leukemia treated with cranial RT, and HL treated with mantle field radiation. In a retrospective cohort study of 2201 5-year survivors of HL, those treated with RT to the neck and mediastinum were particularly at increased risk for stroke and transient ischemic attack. The incidences were higher among patients diagnosed at younger than 21 years than those diagnosed between 21 and 30 years of age. The standardized incidence ratio was 3.8 and 3.1, respectively.

Nephrotoxicity: Long-term renal dysfunction has been reported in survivors of testicular cancer treated with infradiaphragmatic RT and cisplatin-based chemotherapy. In one study with a long-term follow-up, renal impairment was observed in 8% of patients treated with abdominal RT alone compared with a 14% reduction of function in patients treated with chemotherapy with or without RT. Age at treatment and type of treatment were associated with impaired renal function.

Endocrine Complications: Cranial or spinal RT, TBI, and target-organ irradiation involving the neck, abdomen, pelvis, and testes are associated with endocrine late effects in survivors of AYA cancers. The most common endocrine complications include growth hormone (GH) deficiency, thyroid gland abnormalities, gonadal dysfunction, and decreased fertility. AYA cancer survivors treated with an RT dose of 18 Gy or more to the hypothalamic-pituitary-adrenal (HPA) axis are at high risk for GH deficiency, whereas those treated with RT dose of 40 Gy or more to the HPA axis are at risk for developing central hypothyroidism, gonadotropin deficiency, and central adrenal insufficiency.

GH deficiency can be observed within 5 years after treatment with RT doses higher than 30 Gy, whereas in patients treated with lower doses (18–24 Gy) it may not be evident for 10 years or more. Secondary thyroid cancers, hypothyroidism, and, to a lesser extent, hyperthyroidism are more common among AYA survivors of brain tumors, ALL, HL, and those who underwent HSCT. Testicular cancer survivors treated with chemotherapy and RT are at greater risk for hypogonadism. Low testosterone levels and testosterone replacement have been reported in 34% and 4% of testicular cancer survivors, respectively.

Long-Term Follow-Up

AYA cancer survivors have a high risk of developing a wide range of late effects. AYA cancer survivors may benefit from regular screening and early intervention for cardiovascular disease. Continued follow-up of AYA cancer survivors is needed to monitor the pulmonary complications. Development of a “Cancer Treatment Summary and Survivorship Care Plan,” including periodic evaluation with focused history, physical examination, and screening based on treatment exposures and risk for treatment-related late effects, should be an integral part of management of AYA patients with cancer.
The models for AYA survivorship care include cancer center follow-up (primary treatment team or specialized long-term follow-up clinics), follow-up by the patient’s primary care physician, or a combination of both (shared care model). Some studies have shown that a shared care model involving both the primary oncology team and the primary care physician is feasible and can facilitate appropriate care in childhood cancer survivors.

Risk stratification of survivors based on the current medical issues and prior treatments may be helpful to determine the different levels of follow-up in the shared care model. Survivors at low risk for late effects (treated with surgery alone and/or chemotherapy with no radiation, not including alkylating agents, anthracycline, bleomycin, or epipodophyllotoxin) can be transitioned to their primary care physician soon after completion of therapy. Survivors at moderate risk for late effects (treated with low- or moderate-dose chemotherapy containing alkylating agents, anthracycline, bleomycin, or epipodophyllotoxin, with no radiation) can be evaluated by their oncology team or primary care physician on alternating years. Survivors at high risk for late effects, such as those treated for CNS cancers or with a stem cell transplantation, any radiation, high-dose alkylating agents, anthracycline, bleomycin, or epipodophyllotoxin, should be followed up annually by their oncology team and continue follow-up care with their primary care physician.

NCCN Recommendations

The following screening recommendations are adapted from the Children’s Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, available at www.survivorshipguidelines.org. The recommendations are based on the treatment exposure; timing and intensity of screening may be adapted based on additional risk factors.

Cardiovascular Screening:
- Cardiovascular risk assessment and screening are recommended for AYA cancer survivors treated with mediastinal, chest, or abdominal radiation of 30 Gy or more.
- An echocardiogram (or mitigated acquisition [MUGA] scan) every 1 to 2 years is recommended for those treated with anthracycline-based chemotherapy, chest radiation, or combined anthracycline-based chemotherapy and chest radiation.
- Screening for ischemic coronary artery disease remains controversial; cardiology consultation (5–10 years after radiation) in patients who received chest radiation of 40 Gy or more can be considered.

Pulmonary Screening:
- Chest radiograph and pulmonary function tests as a posttherapy baseline, and then as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction, is recommended for all patients treated with chest radiation either alone or in combination with chemotherapy containing bleomycin, busulfan, or carmustine; TBI; and bleomycin-based chemotherapy.

Neuroendocrine Screening:
- Routine neuroendocrine axis screening to monitor GH deficiency, central hypothyroidism, gonadotropin deficiency, and central adrenal deficiency is recommended throughout the entire lifespan of AYA cancer survivors.
- Periodic testing of thyroid function and screening for early detection of thyroid cancer (thyroid stimulating hormone [TSH] and thyroid/neck examination, annually) must be performed on AYA cancer survivors.
- Audiology testing as a posttherapy baseline and then as clinically indicated for signs and symptoms of hearing loss is recommended for patients with cisplatin-based chemotherapy, radiation involving the ear, or a combination of cisplatin-based chemotherapy and cranial/ear radiation.

Neuropsychological Evaluation:
- Severe neurocognitive deficits are uncommon in survivors of AYA cancer, including CNS tumors. However, subtle deficits in executive function, sustained attention, memory, and processing speed may occur with a cranial radiation dose of 18 Gy or more.
- In patients with evidence of impaired educational or vocational progress, formal neuropsychological evaluation is recommended.

Assessment of Renal Function:
- Screening for renal insufficiency and secondary renal/renovascular hypertension is recommended for all patients treated with a radiation dose of 10 Gy or more and a combination of radia-
tion with chemotherapy containing nephrotoxic drugs, such as cisplatin, ifosfamide, aminoglycosides, amphotericin, and immunosuppressants.

- Screening for hemorrhagic cystitis/bladder fibrosis or bladder cancer is recommended for patients treated with cyclophosphamide combined with pelvic irradiation.

**Assessment for Gonadal Function:**

**Men:**
- Analyze semen for evaluation of infertility or as requested by the patient; periodic evaluation over time is recommended, because resumption of spermatogenesis can occur up to 10 years after treatment.
- Monitor testosterone levels as clinically indicated in patients with clinical signs and symptoms of testosterone deficiency.
- See “Impact of Treatment on Fertility and Fertility Preservation,” page 1133.

**Women:**
- Monitor follicle-stimulating hormone, luteinizing hormone, and estradiol levels as indicated in patients with irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency.
- See “Impact of Treatment on Fertility and Fertility Preservation,” page 1133.

**Palliative and End-of-Life Care**

Palliative care involves interdisciplinary care of patients with life-threatening illnesses, both malignant and nonmalignant. The goal of palliative care in a patient with incurable cancer is to control symptoms, relieve suffering from adverse effects of treatment, and improve quality of life for patients and their families, regardless of the disease stage or need for other therapies.\(^{175}\) See 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.\(^{175}\) Introduction of palliative care for symptom management and psychosocial support should occur before the patient is considered “palliative” to provide the best possible care for the patient.\(^{176}\) Palliative care is appropriate even when patients are being treated with curative intent, and consensus is growing that AYA patients should have access to palliative care services from the time of diagnosis until the time of death or cure.\(^{176}\) Patients, caregivers, and health care professionals should be taught that palliative care is an integral part of their comprehensive cancer care. AYA patients usually are not making decisions in isolation. Although some AYA patients have the ability to make life and death decisions independently, many either are not the primary decision-maker or rely intensely on input from parents, spouses, significant others, and other family members.\(^{175}\) Palliative care services should also consider the psychosocial needs of the patient’s family, friends, and caregivers.\(^{176}\) Social support is required for almost all AYA patients receiving palliative care.

End-of-life care involves the management of delirium and existential distress, discussion about the place of death, and support of family.\(^{175}\) AYA patients understand that death is permanent and irreversible. Health care professionals must not assume that AYA patients may be less inclined to discuss death and other end-of-life issues.\(^{175}\) 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 participating in a one-on-one survey administered by a researcher.\(^{177}\) 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.\(^{178}\) In one retrospective review, a significant number of adolescents dying of cancer felt that discussions about the end of life occurred very close to death, thus allowing very little time to psychologically prepare for death.\(^{179}\) The palliative care team can also help relieve physical and emotional suffering and facilitate difficult end-of-life issues, such as nutrition/hydration, sedation, treatment cessation, and place of death.\(^{175}\) An advance care planning document may be appropriate and helpful for terminally ill AYA patients with metastatic cancer.\(^{180}\)

**References**


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### Individual Disclosures for the NCCN Adolescent and Young Adult Oncology Panel

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The NCCN guidelines staff have no conflicts to disclose.