National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Survivorship

Version 1.2015

NCCN.org

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≅ Nutrition science/Dietician
¥ Patient advocacy
€ Pediatric oncology
θ Psychiatry, psychology, including health behavior
£ Supportive care including palliative, pain management, pastoral care, and oncology social work
¶ Surgery/Surgical oncology
ω Urology
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Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

NCCN Guidelines Version 1.2015 Summary Updates Survivorship

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Updates in Version 1.2015 of the NCCN Guidelines for Survivorship from Version 2.2014 include:

Global Changes

- **A new algorithm providing recommendations for the treatment of "Anthracycline-Induced Cardiac Toxicity" (SCARDIO-1) was added to the "Late Effects/Long-Term Psychosocial And Physical Problems" section.**
- **The Discussion text regarding the following sections was updated to reflect the changes in the algorithms: General Principles, Standards of Survivorship Care, Assessment for Effects of Cancer and Its Treatment, Anthracycline-Induced Cardiac Toxicity, and Healthy Lifestyles (Physical Activity, Nutrition and Weight Management, Supplement Use) (MS-1).**

GENERAL SURVIVORSHIP PRINCIPLES

SURV-4 Assessment By Health Care Provider *(Oncology or Primary Care)* At Regular Intervals

- **Title revised: "Assessment By Health Care Provider *(Oncology or Primary Care)* At Regular Intervals"**
- **First bullet revised: "A periodic assessment *at least annually* is recommended for all survivors to determine any needs and necessary interventions. For sample assessment, see SURV-A"**
- **New bullet added: "*Shared coordinated care between the oncology provider and primary care provider is encouraged.*"**
- **Point #3 revised: "Medication *(including over the counter medications and supplements).*"**

SURV-A 1 of 2 Survivorship Assessment

- **Title revised: "Survivorship ~~Baseline~~ Assessment."**
- **Instruction statement revised: "Please answer the following questions regarding possible symptoms that you may have experienced over the past ~~4~~ *2* weeks"**
- **New section added under Survivorship Concerns: "Cardiac Toxicity" with corresponding questions:**
  - ***Did you receive anthracycline therapy (eg, doxorubicin, epirubicin, daunorubicin, AC [doxorubicin + cyclophosphamide])? Yes/No***
  - ***Do you have shortness of breath or chest pain after physical activity or exercise? Yes/No***
  - ***Do you have shortness of breath when lying flat, wake up at night needing to get air, or have persistent leg swelling? Yes/No***
- **Anxiety and Depression:**
  - **The following questions were added:**
    - **Have you been bothered more than half the days by little interest or pleasure in doing things? Yes/No**
    - **Have you been bothered more than half the days by feeling down, depressed, or hopeless? Yes/No**
    - **Have you been bothered more than half the days by not being able to stop or control worrying, or have you felt nervous or on edge? Yes/No**

SURV-A 1 of 2 Survivorship Assessment (continued)

  - **The following questions were removed:**
    - **Do you often feel nervous or do you worry? Yes/No**
    - **Do you often feel sad or depressed? Yes/No**
    - **Have you lost interest in things you used to enjoy? Yes/No**
- **Cognitive Function: Question 7 revised, "Do you have difficulties with multitasking or *paying* attention? Yes/No"**
- **Sexual Function: The following question was added, "*Are these concerns causing you distress? Yes/No*"**
- **Sleep Disorder: The following question was added, "*Have you been told that you snore frequently or that you stop breathing during sleep? Yes/No.*"**
- **Healthy Lifestyle:**
  - **Under "Survivorship Concerns" the title "Physical Activity" changed to "*Healthy Lifestyle.*"**
  - **The following questions were added:**
    - ***Do you engage in regular physical activity or exercise, such as brisk walking, jogging, bicycling, swimming, etc? Yes/No***
      - ***If you answered "Yes", how often?***
    - ***Excluding white potatoes, do you eat at least 2½ cups of fruits and/or vegetables each day? Yes/No***
    - ***During the past 30 days, did you diet to lose weight or to keep from gaining weight? Yes/No***
  - **The following questions were removed:**
    - **Are you exercising or doing some physical activity for less than 150 minutes a week? Yes/No**
    - **Do you have any limitations to participating in the physical activities that you enjoy? Yes/No**
- **Immunizations and Infections: Question 24 revised, "Have you received your flu vaccine this ~~year~~ *flu season*? Yes/No"**

SURV-A 2 of 2 Survivorship Assessment Provider Key
- Page was revised to reflect the changes made to SURV-A 1 of 2.

SURV-B Survivorship Resources for Healthcare Professionals and Patients
- The organizations and links were updated.

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Anxiety and Depression
- The 2015 algorithm update is in progress (SANXDE-1)

Cognitive Function
- The 2015 algorithm update is in progress (SCF-1)

Fatigue

SFAT-3
- History and Physical; Under "Assessment of treatable contributing factors", revised: "Medications (~~consider persistent use of~~ *eg,* sleep aids, pain medications, or antiemetics)."
- Evaluation; Laboratory evaluation; Endocrinologic evaluation:
  - First diamond sub-bullet revised: "~~Consider evaluation of~~ TSH in patients who have received prior head/neck..."
  - New diamond sub-bullet added: "*Cortical stimulation test, if history of prolonged steroid use.*"
  - Imaging: Last bullet revised: "~~Consider~~ Chest x-ray and oxygen saturation testing for pulmonary complaints"

SFAT-4
- Treatment of Contributing Factors; Fourth sub-bullet: Under "Anemia" sub-sub-bullet revised, "Consider referral/futher evaluation for ~~persistent~~ anemia or cytopenias."

SFAT-5
- Patient/Family Education and Counseling: Recommendation revised, "*Provide* information about ~~known~~ patterns of fatigue during and ~~following~~ *after* treatment."
- Physical Activity; Third bullet; Last sub-arrow revised: "For patients with ~~severe~~ fatigue interfering with function...."
- Pharmacologic: Recommendation revised: "Consider psychostimulants (methylphenidate ~~or modafinil~~) after ruling out other causes of fatigue and failure of other interventions"
- Footnote "h" revised: "~~There is more evidence for methylphenidate and less for modafinil. These agents~~ *Methylphenidate* should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded.

Pain

SPAIN-1
- If pain present pathway: "Severe uncontrolled pain is a medical emergency and should be ~~responded to~~ *addressed* promptly"
- Cancer Pain Syndromes: Syndrome name revised: "Chronic ~~postoperative~~ pain syndromes (amputation, neck dissection, mastectomy, *thoracotomy*)"

SPAIN-2 Neuropathic Pain
- Treatment
  - General measures: Corticosteroids were removed from the list of adjuvant analgesics
  - For refractory pain, consider referral to pain...; Local therapies:
    - Pharmacologic therapies: "Intercostal nerve blocks" was removed.
    - Non-pharmacologic therapies; The following therapies were added:
      - *Neurotomy with radiofrequency ablation*
      - *Consider transcutaneous electrical nerve stimulation (TENS) unit*
      - *Consider dorsal column stimulation*

SPAIN-3 Chronic Pain Syndrome
- Treatment:
  - Bullet revised, "For refractory pain, consider referral to pain management services...and/or rehabilitation *for services such as*: "~~Consider~~ TENS unit,; ~~Consider~~ dorsal column stimulation..."
  - "Intercostal nerve blocks" was removed as an option for refractory pain.
- Third column; Revised: "Specific ~~postoperative~~ *chronic* pain syndromes
- Revised: "For post-mastectomy *or post-thoracotomy* syndrome."

SPAIN-4 Myalgias, Arthralgias
- Nonpharmacologic: "Exercise" changed to "*Physical activity.*"

LATE EFFECTS/LONG-TERM PSYCHOSOCIAL AND PHYSICAL PROBLEMS

Pain

SPAIN-5 Skeletal Pain

- Vertebral compression; General measures: First bullet revised, "Vitamin D/*bisphosphonates.*"
- Avascular necrosis: "Cement augmentation for fractures" removed
- Osteonecrosis of the jaw: Revised, "~~Consider~~ Referral to oral surgeon"

SPAIN-6 Myofascial pain

- This page was extensively revised including:
  - Last bullet; "Muscle cramps, spasms"; First arrow sub-bullet: "hydration status" was added to list of tests.
  - Physical therapy was added as an option.

SPAIN-7 Gastrointestinal/Urinary/Pelvic Pain

- New bullet for "Gastrointestinal pain" was added.
- Chronic pain:
  - "*Consider referreal to urologist or gynecologist*" added
  - Second sub-arrow revised: "Consider physical therapy for pelvic floor ~~strengthening~~ exercises"
  - "Analgesics" was removed.
- Dyspareunia
  - "*Consider referral to gynecologist or sexual health specialist*" added.

SPAIN-8 Lymphedema

- Recommendation "Consider referral to lymphedema specialist" changed to "Referral to lymphedema specialist, *if available.*"
- Compression garments: The following were added, "*Review fit and age of garments, Review use of garments, Ask about weight changes*"

SPAIN-9 Post-radiation Pain

- Treatment: Recommendation revised, "Pain medication *(non-opioid medications such as antiepileptics, NSAIDs).*"

SPAIN-A Principles of Opioid Use in Long-Term Survivors

- First bullet revised: "Use the lowest opioid dose *for the shortest period of time* possible, if opioids are necessary."
- Under Endocrine/hypopituitary abnormalities, "*Testosterone deficiency*" was added.

Sexual Function (Female)

- The 2015 algorithm update is in progress (SSFF-1)

Sexual Function (Male)

- The 2015 algorithm update is in progress (SSFM-1)

Sleep Disorders

- The 2015 algorithm update is in progress (SSD-1)

PREVENTIVE HEALTH

Healthy Lifestyles

HL-1 General Principles of Healthy Lifestyles

- Third bullet:
  - First sub-arrow; Second diamond sub-bullet: Revised, "~~Calculate and monitor~~ *Achieve and maintain a normal* body mass index (BMI) (SNWM-A)."
  - First arrow sub-bullet; Third diamond sub-bullet:"*Weigh oneself weekly to monitor weight gain/loss*" was added.
  - Second sub-arrow; Under "Engage in physical activity regularly"
    - First diamond sub-bullet revised: "Avoid inactivity ~~and a sedentary lifestyle~~; *engage in general physical activity daily (ie, taking the stairs, parking in the back of parking lot)*"
    - Third arrow sub-bullet revised: "Maintain a healthy diet high in fruits, vegetables, and whole grains *and low in red and processed meats, sugars, and fats in order to promote weight control and avoid obesity*."
- New bullet added to page, "W*ork with primary care to set incremental goals for diet, physical activity, and weight management.*"

Physical Activity

SPA-1 General Principles of Physical Activity

- New bullet and sub-bullet added: "*Avoid inactivity; engage in general physical activity daily. Physical activity includes exercise, daily routine activities, and recreational activities."*
- Under "General recommendations for cancer survivors"; Third arrow sub-bullet: Revised, "Stretch major muscle groups on ~~days exercises are performed~~ *a routine basis* ."
- The following bullets were deleted:
  - All survivors should be encouraged to avoid inactivity or a sedentary lifestyle and return to daily activities as soon as possible
  - Patients who are able should be encouraged to engage in physical activity daily.
- Footnote deleted: "Physical activity includes exercise, daily routine activities, and recreational activities."

Physical Activity (continued)

SPA-3 Risk Assessment for Physical Activity-Induced Adverse Events

- Low Risk: "Early stage cancer survivors" removed from the list.
- Moderate Risk: Second bullet revised, "~~Bone metastases~~/Poor bone health."
- High Risk: "*Worsening/changing physical condition (ie, lymphedema exacerbation)*" was added to the list. Previously it was under "Avoid Physical Activity/Exercise"
- The section "Avoid Physical Activity/Exercise" was removed.
- Footnote removed: "Avoid unsupervised physical activity for approximately 6 weeks. However, supervised physical activity with early mobilization and referral to a trained therapist is strongly encouraged."

SPA-4 Implementation of Recommendations

- Third column; Bottom pathway:
  - New bullet added: "*Survivors and providers should work together to develop incremental short- and long-term goals regarding physical activity participation. These may include incremental increases in time spent in physical activity or in intensity of activity.*."
  - Second bullet revised, "*Suggested* initial prescription..."

SPA-A Considerations for Specific Populations

- Stem cell transplant: "Avoid hot tubs for one year after transplant" was removed.
- The last bullet, "Bone loss/bone metastases" changed to "*Poor bone health*".

PREVENTIVE HEALTH

Nutrition and Weight Management

SNWM-1 General Principles of Nutrition

- Third bullet; Recommended composition of diet
  - First arrow sub-bullet revised, ~~"For most survivors recommending the USDA "MyPlate"(2/3 plant sources, 1/3 animal sources www.choosemyplate.gov) is sufficient.~~
    - *2/3 (or more) vegetables, fruits, whole grains, or beans*
    - *1/3 (or less) animal protein*
- Last bullet revised: "...Thus, moderate consumption *(3 or less servings per day)* of soy foods is considered prudent."
- New footnotes added:
  - "a": *Recommendation for healthy food portion sizes can be found on the American Institute of Cancer Research (AICR) website (http://www.aicr.org/new-american-plate/reduce_diet_new_american_plate_portion.html) as well as the USDA "Choose My Plate" website www.choosemyplate.gov.*
  - "b"*: Encourage the use of healthy recipes from resources such as the American Cancer Society's "Find Healthy Recipes" website: http://www.cancer.org/healthy/eathealthygetactive/eathealthy/findhealthyrecipes/maindishes/index*
  - "c": *For patients desiring more precise recommendations for dietary composition guidelines:*
    - *Fat: 20%–35% of total energy intake with saturated fat <10% and trans fat <3%;*
    - *Carbohydrates : 45%–65% of total intake with high intake of fruits, vegetables, and whole grains;*
    - *Protein: 10%–35% of total intake and goal of 0.8 g/kg*

    (note that this information was previously in the algorithm)

SNWM-3 Nutrition and Weight Management Assessment

- New footnote "g" added: "*For additional resources see the ASCO Toolkit on Obesity and Cancer: http://www.asco.org/practice-research/obesity-and-cancer and the LIVESTRONG My Plate Calorie Tracker: http://www.livestrong.com/myplate.*"

Immunizations and Infections

SIMIN-1 General Principles of Immunizations

- First bullet revised: "These principles apply to *cancer* survivors, *including those with* hematologic or solid tumor malignancies ~~including~~ *and those post* transplant ~~survivors~~."

SIMIN-2

- Risk Assessment and Screening; Risk factors for infections; Third bullet revised, "Monoclonal antibodies *(eg, rituximab, alemtuzumab)*"
- Interventions: The bullet "Education on infection prevention practices" and its corresponding sub-bullets were moved to the top of the list.
- Footnote "h": Statement added, "*For guidelines on physical activity see (SPA-1).*"

SIMIN-3

- Inactivated, purified antigens or Bacteria components; Recommended for all cancer survivors; Treatment:
  - Second bullet revised: "Pneumococcal ~~polysaccharide~~ vaccine"
  - Last bullet revised: "Human papillomavirus (HPV) in previously unvaccinated females and males *between 11–26 years of age.*"

SIMIN-A General Principles of Vaccines in Cancer Survivors

1 of 3 Vaccination in Non-Transplant Survivors

- Last arrow sub-bullet revised: "Consider human papillomavirus (HPV) vaccine in survivors ~~≤ 26 years~~ *11–26 years of age.*"

SIMIN-B

- New section added: "*Vaccines That Can Be Used With Caution In Close Contacts of Immunocompromised Survivors.*"
- New footnotes added:
  - *Rubin et al, 2013 IDSA Clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.*
  - *Immunocompromised patients should avoid contact with persons who develop skin lesions after receipt of Varicella or Zoster vaccine, until the lesions clear.*

General Survivorship Principles

DEFINITION OF SURVIVORSHIP

- **An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also impacted.[a]**
- **These guidelines focus on the vast and persistent impact both the diagnosis and treatment of cancer have on the adult survivor. This includes the potential impact on health, physical and mental states, health behaviors, professional and personal identity, sexuality, and financial standing.**

STANDARDS FOR SURVIVORSHIP CARE[b]

Care of the cancer survivor should include:

1. **Prevention of new and recurrent cancers and other late effects**
2. **Surveillance for cancer spread, recurrence, or second cancers**
3. **Assessment of late psychosocial and physical effects**
4. **Intervention for consequences of cancer and treatment (eg, medical problems, symptoms, psychologic distress, financial and social concerns)**
5. **Coordination of care between primary care providers and specialists to ensure that all of the survivor's health needs are met.**

[a] Adapted with permission from the National Coalition for Cancer Survivorship as shown in the National Cancer Institute's Office of Cancer Survivorship Definitions web page available at http://cancercontrol.cancer.gov/ocs/statistics/definitions.html.

[b] From Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Committee on Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine and National Research Council 2006. Available at: http://www.nap.edu/catalog/11468.html

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

GENERAL PRINCIPLES OF THE SURVIVORSHIP GUIDELINES

- These guidelines are focused on survivors after the completion of cancer treatment and in clinical remission.
- These guidelines are designed to provide a framework for the general survivorship care and management of potential long-term and/or late effects of cancer and its treatment that survivors may experience.
- The NCCN Guidelines for Survivorship should be used as a supplement to the follow-up recommendations within the disease-specific guidelines. See the NCCN Guidelines for Treatment of Cancer by Site and NCCN Guidelines for Palliative Care for recommendations regarding metastatic disease.
- The panel does not assume that all survivorship issues will be addressed at every visit. The panel recommends periodic screening assessments and appropriate follow-up care as clinically indicated.
- These guidelines provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment, and are intended for health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in both the oncology and primary care practices.
- These guidelines, with the appropriate disease-specific guideline, provide a framework for the coordination of care between the survivor's health care providers to insure that needs are appropriately addressed.
- The topics, assessments, and interventions may also be applicable to those survivors living with metastatic disease, as clinically appropriate. (Also see the NCCN Guidelines for Supportive Care Table of Contents).
- For survivorship issues related to younger populations, see the NCCN Guidelines for Adolescent and Young Adults and the Children's Oncology Group Childhood Survivorship guidelines (www.survivorshipguidelines.org).

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SCREENING FOR SECOND CANCERS

- **Subsequent malignant neoplasms may occur in survivors, due to genetic susceptibilities (ex, cancer syndromes), shared etiologic exposures (ex, smoking, environmental exposures) and mutagenic effects of cancer treatment.**
- **The overall cancer rate in survivors is higher than in the general population.**
- **Treatment-related subsequent primary cancers vary with the type and intensity of anticancer treatment and are associated in particular with radiation and specific chemotherapeutic agents.**
- **Screening for second primary cancers should be a shared responsibility between primary and oncology care physicians (See the NCCN Guidelines for Detection, Prevention, and Risk Reduction Table of Contents).**

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ASSESSMENT BY HEALTH CARE PROVIDER (ONCOLOGY OR PRIMARY CARE) AT REGULAR INTERVALS

- **A periodic assessment at least annually is recommended for all survivors to determine any needs and necessary interventions. For sample assessment, see SURV-A.[c]**
- **Shared coordinated care between the oncology provider and primary care provider is encouraged.**
- **Care providers are also encouraged to assess the following at regular intervals to determine whether reversible or contributing causes for symptoms exist:**

1. **Current disease status**
2. **Functional/performance status**
3. **Medication (including over the counter medications and supplements)**
4. **Comorbidities (including weight and tobacco use)**
5. **Prior cancer treatment history and modalities used**

[c]This is a sample assessment tool. While this instrument has not yet been piloted or validated, the answers can be used to guide providers to topics within the guidelines that require more in-depth assessment. Validation of the best way to assess survivorship issues is ongoing.

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SURVIVORSHIP ASSESSMENT (Patient version)

Please answer the following questions regarding possible symptoms that you may have experienced over the past 2 weeks:

Survivorship Concerns	Survivorship Care Survey
Cardiac Toxicity	1. Did you receive anthracycline therapy (eg, doxorubicin, epirubicin, daunorubicin, AC [doxorubicin + cyclophosphamide])? Yes/No 2. Do you have shortness of breath or chest pain after physical activity or exercise? Yes/No 3. Do you have shortness of breath when lying flat, wake up at night needing to get air, or have persistent leg swelling? Yes/No
Anxiety and Depression	4. Have you been bothered more than half the days by little interest or pleasure in doing things? Yes/No 5. Have you been bothered more than half the days by feeling down, depressed, or hopeless? Yes/No 6. Have you been bothered more than half the days by not being able to stop or control worrying, or have you felt nervous or on edge? Yes/No
Cognitive Function	7. Do you have difficulties with multitasking or paying attention? Yes/No 8. Do you have difficulties with remembering things? Yes/No 9. Does your thinking seem slow? Yes/No
Fatigue	10. Do you feel persistent fatigue despite a good night's sleep? Yes/No 11. Does fatigue interfere with your usual activities? Yes/No 12. How would you rate your fatigue on a scale of 0 (none) to 10 (extreme) over the past month? 0–10
Pain	13. Are you having any pain? Yes/No 14. How would you rate your pain on a scale of 0 (none) to 10 (extreme) over the past month? 0–10
Sexual Function	15. Are you dissatisfied with your sexual function? Yes/No 16. Do you have any concerns regarding sexual function, sexual activity? Yes/No 17. Are these concerns causing you distress? Yes/No
Sleep Disorder	18. Are you having problems falling asleep or staying asleep? Yes/No 19. Are you experiencing excessive sleepiness (ie, sleepiness or falling asleep in inappropriate situations or sleeping more during a 24-hour period than in the past)? Yes/No 20. Have you been told that you snore frequently or that you stop breathing during sleep? Yes/No
Healthy Lifestyle	21. Do you engage in regular physical activity or exercise, such as brisk walking, jogging, bicycling, swimming, etc? Yes/No ▸ 21a. If you answered "Yes", how often? 22. Excluding white potatoes, do you eat at least 2½ cups of fruits and/or vegetables each day? Yes/No 23. During the past 30 days, did you diet to lose weight or to keep from gaining weight? Yes/No
Immunizations and Infections	24. Have you received your flu vaccine this flu season? Yes/No 25. Have you received any vaccinations recently? Yes/No

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SURVIVORSHIP ASSESSMENT*
(Provider Key)

Please answer the following questions regarding possible symptoms that you may have experienced over the past 2 weeks:

Survivorship Concerns	Survivorship Care Survey	Provider Key
Cardiac Toxicity	Questions 1–3	If YES to any question, refer to SCARDIO-1
Anxiety and Depression	Questions 4–6	If YES to any question, refer to SANXDE-1
Cognitive Function	Questions 7–9	If YES to any question, refer to SCF-1
Fatigue	Questions 10–12	If YES to either question 10 or 11, or a rating of >3 to question 12, refer to SFAT-1
Pain	Questions 13–14	If YES to question 13 and a rating of >4 to question 14, refer to SPAIN-1
Sexual Function	Questions 15–17	If YES to any question, refer to SSFF-1 (female) or SSFM-1 (male)
Sleep Disorder	Questions 18–20	If YES to any question, refer to SSD-1
Healthy Lifestyle	Questions 21–23	If NO to question 21 or 22; or YES to question 23, OR if question 21a is less than 3 times per week, OR if BMI not in the healthy range (See SNWM-A), refer to HL-1
Immunizations and Infections	Questions 24–25	If NO to either question, refer to SIMIN-1

*This is a sample assessment tool. While this instrument has not yet been piloted or validated, the answers can be used to guide providers to topics within the guidelines that require more in-depth assessment. Validation of the best way to assess survivorship issues is ongoing.

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SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS*

General Online Information	
National Coalition for Cancer Survivorship (NCCS)	http://www.canceradvocacy.org/
American Association for Cancer Research (AACR) • A six-part podcast series about survivorship in partnership with CR Magazine and The Wellness Community:	http://www.aacr.org/ http://www.crmagazine.org/archive/Crpodcasts/Pages/SurvivingThriving.aspx
American Cancer Society • Survivorship information • Cancer Survivors Network • National Cancer Survivorship Resource Center • Physical Side Effects information, including sexual function	http://www.cancer.org/index http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index http://csn.cancer.org/ http://www.cancer.org/SurvivorshipCenter http://www.cancer.org/treatment/treatmentsandsideeffects/physicalsideeffects/index
American Institute for Cancer Research (AICR): Survivorship information	http://www.aicr.org/patients-survivors/after-cancer-treatment.html
ASCO: Survivorship information	http://www.cancer.net/survivorship
Cancer Care: Free, professional support services for anyone affected by cancer	www.cancercare.org
Centers for Disease Control and Prevention: Survivorship information	http://www.cdc.gov/cancer/survivorship/index.htm
Leukemia & Lymphoma Society: Survivorship information	http://www.lls.org/diseaseinformation/managingyourcancer/survivorship/
LIVESTRONG	http://www.livestrong.org/
National Cancer Institute: Cancer Survivorship Research • Facing Forward series, designed to educate cancer survivors, family members, and health care providers about the challenges associated with life after cancer treatment	http://survivorship.cancer.gov http://cancercontrol.cancer.gov/ocs/resources/ffseries.html
National Comprehensive Cancer Network (NCCN) • Life After Cancer: Patient and Caregiver Resources and Information	http://www.nccn.org/index.asp http://www.nccn.org/patients/resources/life_after_cancer/
MedlinePlus: Current accurate information by cancer site	http://www.nlm.nih.gov/medlineplus/cancers.html
Help Lines	
American Cancer Society	1-800-227-2345
American Psychosocial Oncology Society	1-866-276-7443
Cancer Support Community	1-888-793-9355 https://csc.cancerexperienceregistry.org/
LIVESTRONG SurvivorCare	1-855-220-7777
National Cancer Institute's Cancer Information Service	1-800-4-CANCER
Other Survivorship Guidelines	
Children's Oncology Group: Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers	http://www.survivorshipguidelines.org/

*There are many smart phone/tablet/mobile device apps, web-based programs, DVDs, and TV programs available to help survivors with various aspects of health care and wellness.

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SURVIVORSHIP RESOURCES FOR HEALTH CARE PROFESSIONALS AND PATIENTS* (continued)

Survivorship Care Planning	
ASCO Cancer Treatment Summaries	http://www.cancer.net/survivorship/follow-care-after-cancer-treatment/asco-cancer-treatment-summaries
Journey Forward: Resources for survivorship care planning	http://www.journeyforward.org/
LIVESTRONG Care Plan	http://www.oncolink.org/oncolife/
Legal and Employment Issues	
Cancer and Careers: Patient information about working and dealing with cancer	http://www.cancerandcareers.org/en
National Coalition for Cancer Survivorship (NCCS) Employment Rights, "Working It Out" Publication	http://www.canceradvocacy.org/resources/employment-rights/
National Coalition for Cancer Survivorship (NCCS) "What Cancer Survivors Need To Know about Health Insurance" Publication	http://www.canceradvocacy.org/resources/health-insurance/
Physical Activity	
American Cancer Society • Nutrition and Physical Activity Guidelines for Cancer Survivors, Patient Page • "Physical Activity and the Cancer Patient" guide	http://onlinelibrary.wiley.com/doi/10.3322/caac.21146/pdf http://www.cancer.org/treatment/survivorshipduringandaftertreatment/stayingactive/physical-activity-and-the-cancer-patient
American College of Sports Medicine: ACSM ProFinder: Search for Certified Professionals	http://members.acsm.org/source/custom/Online_locator/onlinelocator.cfm
Cancer Supportive and Survivorship Care: Exercise: A Cancer Survivor's Tool For Wellness	http://www.cancersupportivecare.com/whyexercise.html
LIVESTRONG at the YMCA	http://www.livestrong.org/YMCA
SilverSneakers: A program that helps older adults live healthy, active lifestyles	https://www.silversneakers.com/
Nutrition and Weight Management	
ASCO Obesity and Cancer Toolkit	http://www.asco.org/practice-research/obesity-and-cancer
Cancer Nutrition Consortium: Nutritional Guidance & Support	http://www.cancernutritionconsortium.org/
LIVESTRONG MYPLATE Calorie Tracker	http://www.livestrong.com/myplate
National Heart, Lung, and Blood Institute • Guideline for the Management of Overweight and Obesity in Adults • 3 Steps to Initiate Discussion About Weight Management With Your Patients	http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/obesity-evidence-review http://www.nhlbi.nih.gov/health/prof/heart/obesity/aim_kit/steps.pdf
Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics	http://www.oncologynutrition.org/
Cardiovascular Health	
American Heart Association/American Stroke Association Tools	http://millionhearts.hhs.gov/resources/tools.html
Smoking Cessation	
American Cancer Society: Smoking cessation support	http://www.cancer.org/healthy/stayawayfromtobacco/index
ASCO: Tobacco Cessation and Control Resources	http://www.asco.org/practice-research/tobacco-cessation-and-control-resources
U.S. Federal Government: Smoking cessation support	http://www.smokefree.gov/

*There are many smart phone/tablet/mobile device apps, web-based programs, DVDs, and TV programs available to help survivors with various aspects of health care and wellness.

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Late Effects/Long-Term Psychosocial and Physical Problems

PRINCIPLES OF ANTHRACYCLINE-INDUCED CARDIAC TOXICITY

- **Cancer treatments can result in diverse cardiovascular issues. These guidelines focus specifically on heart failure or cardiomyopathy that may arise from anthracycline therapy. Other systemic therapies may also cause cardiomyopathy (eg, HER2-targeted therapies), and some of the concepts presented in these recommendations may apply to these other cardiomyopathies.**
- **Anthracycline-induced heart failure may take years or even a decade to manifest. Data suggest that signs of cardiac dysfunction can be seen prior to onset of symptoms. If detected early, anthracycline-induced heart failure may be responsive to cardioprotective medications, although prospective studies evaluating these medications are lacking.**
- **Survivors may have risk factors that predispose them to heart failure (such survivors are considered to have Stage A heart failure) or may have structural heart disease (such survivors are considered to have Stage B heart failure) even if they have no actual symptoms. A history of anthracycline exposure is a risk factor that classifies a survivor as having Stage A heart failure. (defined on SCARDIO-3)**
- **Having a history of anthracycline exposure plus additional cardiovascular risk factors increases the risk for progressive heart failure. It is encouraged that such survivors should have heart failure risk factors, including hypertension, dyslipidemia, and diabetes addressed in coordination with primary care.**
- **The risk for cardiovascular problems varies greatly depending on the type of anthracycline used and the cumulative dose received.**
- **For these guidelines, the panel has placed an emphasis on early recognition and prevention of clinical heart failure, as well as early treatment of patients at risk with appropriate cardioprotective medications to prevent cardiac remodeling over time. Therefore, for high-risk survivors, the panel emphasizes the need for a thorough clinical screening for heart failure within one year after completion of anthracycline therapy**

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INITIAL CLINICAL ASSESSMENT FOR PATIENTS WHO HAVE RECEIVED PREVIOUS ANTHRACYCLINE THERAPY

- History and physical
  - Assess for signs and symptoms of heart failure[a]
  - Assess patient's ability to perform routine and desired activities of daily living
  - Look for signs of volume overload
- Evaluate for presence of heart failure risk factors
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Family history of cardiomyopathy
  - Age >65 years
  - History of other cardiovascular comorbidities (ie, atrial fibrillation, known coronary artery disease [CAD], or baseline evidence of structural heart disease)
- Review other cardiovascular risk factors
  - Smoking
  - Alcoholism
  - Obesity
  - Family history of cardiomyopathy or other heart disease
- Review medications
- Review oncologic history
  - Review total cumulative dose of anthracycline
  - Other systemic therapy[b] and/or chest radiation therapy

→

- Cardiovascular risk factor management[c]
- Consider two-dimensional echocardiogram with doppler flow study for survivors with one or more cardiac risk factors within 1 year after completion of anthracycline therapy[d,e]

→ No evidence of structural heart disease, but symptomatic[2]
- Workup for other causes of symptoms
- Referral to other specialties (eg, pulmonology or cardiology)

→ No evidence of structural heart disease and asymptomatic
or
No echocardiogram performed and asymptomatic

→ See Stage A (SCARDIO-3)

→ Evidence of structural heart disease (asymptomatic or symptomatic[2]):
- Evidence of left ventricular (LV) dysfunction
- Evidence of LV hypertrophy
- Valvular disease

→ Determine stage of cardiomyopathy (heart failure)
See SCARDIO-3

[a] Signs and symptoms of heart failure include: Shortness of breath or chest pain after physical activity or exercise, shortness of breath when sleeping, waking up at night due to shortness of breath, and swelling in the legs.

[b] Trastuzumab, pertuzumab (other Her2 targeted therapy), VEGF signaling pathway (VSP) inhibitors, taxanes in combination with anthracyclines.

[c] Encourage primary care provider involvement in treatment of cardiovascular risk factors and encourage routine follow-up in coordination with primary care provider.

[d] Cardiac risk factors include age >65 years, high cumulative anthracycline dose (ie, cumulative doxorubicin dose of 300 mg/m^2 or equivalent), underlying cardiovascular disease/risk factors, or a low-normal LVEF (50%–54%) at baseline. Patients with symptoms of heart failure should receive an echocardiogram.

[e] Referral to cardiologist/cardio-oncologist if there are echocardiographic abnormalities.

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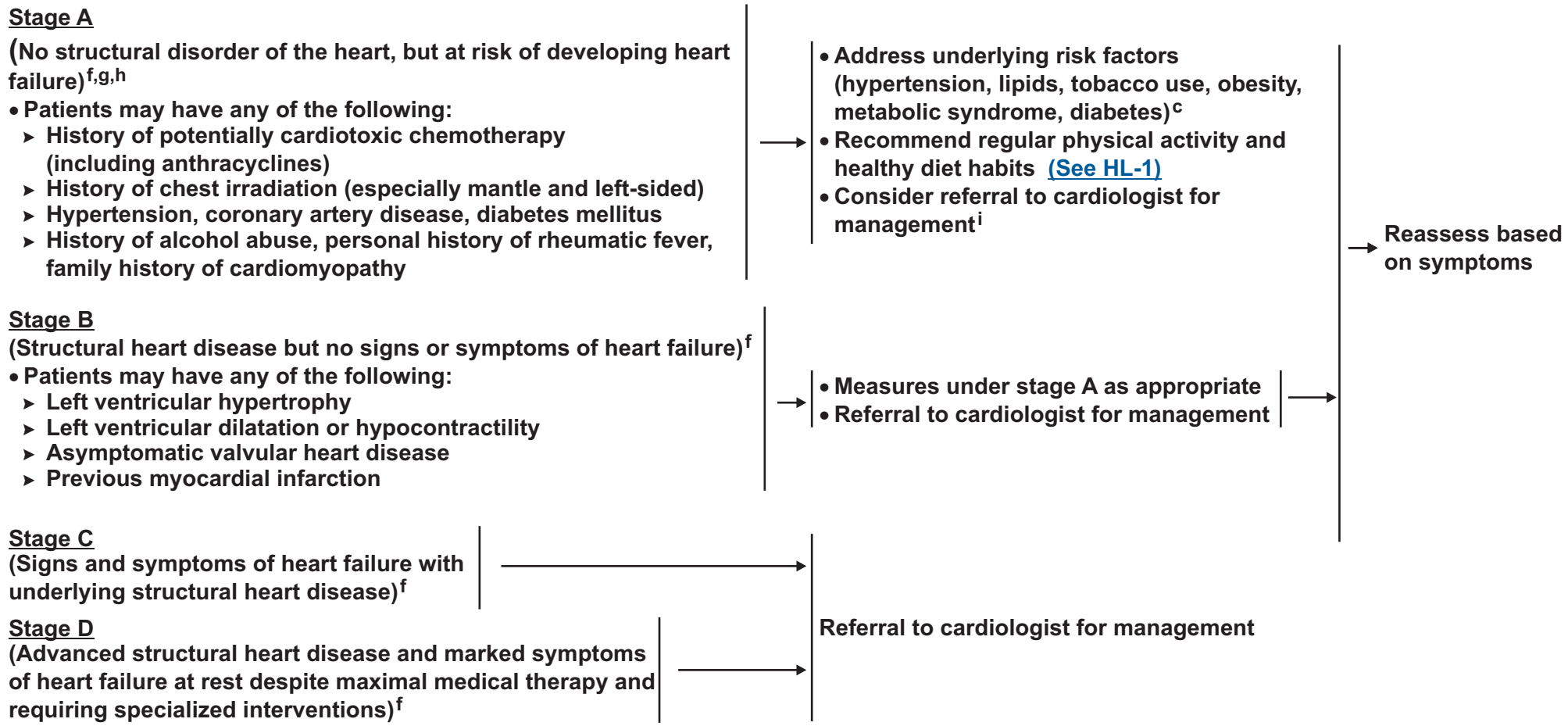

[c]Encourage primary care provider involvement in treatment of cardiovascular risk factors and encourage routine follow-up in coordination with primary care provider.
[f]Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the Amercian College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240-e327.
[g]The use of biomarkers should be considered in select patients at high risk for heart failure (Stage A).
[h]Any patient who has received potentially cardiotoxic chemotherapy and/or chest radiation (and specifically anthracycline-based chemotherapy) should be considered Stage A cardiomyopathy.
[i]Consider referral to a cardiologist, especially if additional anthracycline therapy or other cardiotoxic treatment is needed.

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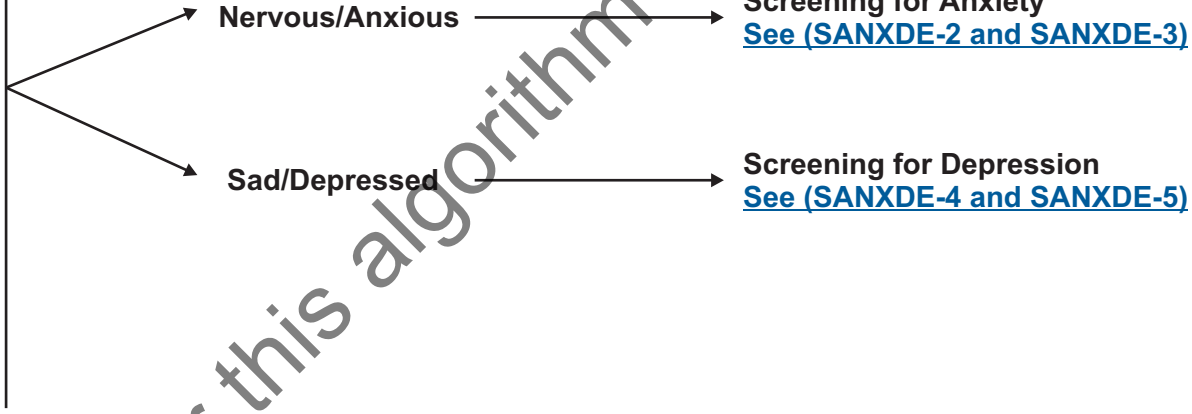
SCREENING: ANXIETY AND DEPRESSION[a]

Screening questions[b] to be asked at regular intervals, especially when there is a change in clinical status or treatment, or patient presents with multiple somatic complaints:

- **Do you feel nervous, or do you worry?**
- **Do you worry that your cancer will recur?**
- **Do you have trouble controlling your worry?**
- **Do you have trouble sleeping? (eg, staying asleep, falling asleep, too much sleep)[b]**
- **Do you have difficulty concentrating?**
- **Do you have less interest or enjoyment in activities?**
- **Do you feel sad or depressed?**
- **Are you having difficulty performing daily activities because of these (above mentioned) feelings or problems?**

Also see NCCN Distress Thermometer Screening Tool (DIS-A)



[a]Survivors of cancer treatment are at especially high risk for anxiety and depression due to the multiple stressors, vulnerabilities, and challenges they face. Most commonly, fear of recurrence leads to anxiety related to surveillance and physical symptoms that may or may not be related to the cancer diagnosis. Because such distress in the setting of unpredictable outcomes can lead to debilitating, but treatable, anxiety and depression, survivors should be closely monitored, especially at times of transition, surveillance, significant loss, major life events, and social isolation.

[b]A positive response to any of the questions should result in further assessment. However, if a patient has an isolated problem with sleep in the absence of other symptoms, refer to the Sleep Disorders Guidelines (SSD-1).

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SCREENING: ANXIETY

DIAGNOSIS

Excessive anxiety and worry that is difficult to control:
- **Sleep disturbance**
- **Restlessness**
- **Muscle tension**
- **Irritability**
- **Difficulty concentrating or mind going blank**
- **Easily fatigued**

→ **General anxiety disorder or Adjustment disorder[d] with anxious mood** → **Safety evaluation[e]** → **See Evaluation (SANXDE-6)**

Acute onset of ≥4 of the following:[c]
- **Palpitations, pounding heart**
- **Sweating, chills, or hot flushes**
- **Trembling or shaking**
- **Sensations of shortness of breath or of choking**
- **Chest discomfort or pain**
- **Nausea**
- **Feeling dizzy, lightheaded, unsteady**
- **Feelings of unreality or being detached from oneself**
- **Fear of dying**
- **Fear of losing control**
- **Paresthesias**

→ **Panic disorder** → **Safety evaluation[e]** → **See Evaluation (SANXDE-6)**

[c] Consideration should be taken for evaluation of other medical causes to rule out alternative etiologies.
[d] Development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s). (American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. 4th rev. ed. Washington, DC: American Psychiatric Association, 2000).
[e] See Safety Evaluation for Anxiety and Depression (SANXDE-A).

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SCREENING: ANXIETY

DIAGNOSIS

- **Exposure to traumatic event[e] and:**
  - **Recurrent intrusive memory of the trauma**
  - **Recurrent dreams of the event**
  - **Feeling as if trauma is recurring**
- **Avoidance of stimuli associated with trauma and numbing of general responsiveness and:**
  - **Inability to recall traumatic events**
  - **Feeling of detachment from others**
  - **Restricted range of emotional expression**
  - **Sense of foreshortened future**
- **Increased arousal: hypervigilence, exaggerated startle, irritability, difficulty concentrating, sleep disturbance**

→ **Post-traumatic stress disorder** → **Safety evaluation[d]** → **See Evaluation (SANXDE-6)**

- **Recurrent persistent thoughts, impulses, or images that cause marked distress and that the person attempts to suppress with some other thought or action**
- **Repetitive behaviors or mental acts that person is compelled to perform in response to an obsession, aimed at reducing stress or preventing some dreaded event**

→ **Obsessive-compulsive disorder** → **Safety evaluation[d]** → **See Evaluation (SANXDE-6)**

[d] See Safety Evaluation for Anxiety and Depression (SANXDE-A).

[e] Person must either be the target of or witness to a traumatic event that threatens the physical integrity to self or other and renders the individual helpless and in fear. A cancer diagnosis or recurrence typically does not qualify as a traumatic event that could lead to a diagnosis of post traumatic stress disorder (PTSD). However, if an individual is exposed to a treatment or intervention that results in severe distress or physical pain, symptoms similar to those of PTSD could emerge if the individual is later subjected to or reminded of this painful experience. If an individual has a history of PTSD prior to a cancer diagnosis and undergoes a treatment or intervention that is especially distressing or painful, symptoms of PTSD could develop in this individual should they be reminded simultaneously of a prior traumatic event.

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SCREENING: DEPRESSION[f,g]

Two weeks or more of depressed mood or loss of interest/pleasure and ≥5 of the following:
- **Feeling sad or empty**
- **Tearfulness**
- **Anhedonia**
- **Unintentional weight loss**
- **Sleep disturbance, insomnia, or hypersomnia**
- **Psychomotor agitation or retardation**
- **Decreased energy**
- **Feelings of worthlessness or excessive guilt**
- **Decreased concentration, indecisiveness**
- **Recurrent thoughts of death, suicidal ideation**

→ **Major depressive disorder (MDD)** →

DIAGNOSIS

Safety evaluation[d]

and

Consider symptoms of mania or history of mania:
- **At least one week of:**
  - **Irritable or expansive mood**
  - **Rapid pressured speech**
  - **Racing thoughts**
  - **Grandiosity**
  - **Decreased need for sleep**
  - **Impulsivity**
  - **Increased goal-directed activity**

and

Consider symptoms of psychosis:
- **Paranoia**
- **Persecutory delusions**
- **Auditory hallucinations**
- **Delusions with typical depressive themes (ie, guilt, worthlessness)**

Safety risk, mania, or psychotic features → **Refer to psychiatrist**

No safety risk, mania, or psychotic features → **See Evaluation (SANXDE-6)**

[d] See Safety Evaluation for Anxiety and Depression (SANXDE-A).

[f] Recommended Assessment Tools:
- Screening Tools: PHQ-9 vs. PHQ-2. The PHQ-2 is comprised of the first two items of the PHQ-9 and can be used as an initial depression screening. If the patient responds affirmatively to either of these two items, the remaining 7 items are asked. (Available at: www.phqscreeners.com/pdfs/02_PHQ-9/English.pdf and http://www.commonwealthfund.org/usr_doc/PHQ2.pdf).

[g] When screening, also take into consideration a patient's cultural differences at presentation (ie, somatization as expression of emotional distress).

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SCREENING: DEPRESSION **DIAGNOSIS**

Depressive features that do not meet the criteria of major depressive disorder → **Depression not otherwise specified** → **Safety evaluation**[d] → **See Evaluation (SANXDE-6)**

Development of emotional or behavioral symptoms in response to an identifiable stressor(s) occuring within 3 months of the onset of the stressor(s) → **Adjustment disorder with depressed mood or with Mixed depressed mood and anxiety** → **Safety evaluation**[d]

- **Moderate/severe adjustment disorder** → **See Evaluation (SANXDE-6)**
- **Mild adjustment disorder** →
  - **Follow-up to reassess**
  - **Consider therapy**
  - **No medications necessary**

[d] See Safety Evaluation for Anxiety and Depression (SANXDE-A).

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EVALUATION: ANXIETY AND DEPRESSION

Medical Factors (H&P Exam)

- General review:
  - Illness status/progression
  - Medication changes/side effects
  - Presence of new or poorly controlled symptoms (ie, pain, nausea, constipation)
  - Status of coexisiting medical conditions (ie, cardiovascular disease, diabetes mellitus, substance abuse)
  - History of prior major depression or anxiety disorder
  - Fatigue level
  - Functional status
  - Current coping strategies
- Laboratory studies to consider:
  - Metabolic (calcium, glucose, uremia, hepatitis)
  - Infection
  - Anemia
    - Vitamin B_{12} deficiency
  - Endocrine
    - Thyroid disease
    - Menopause/hypogonadism, sexual dysfunction, infertility
- Other studies:
  - Neurologic: CNS imaging (rule out metastases, stroke, underlying neurologic disorder); neuropsychological testing to determine cognitive status
  - Cardiac: EKG, ECHO, stress test
  - Pulmonary: Sleep study to rule out obstructive sleep apnea; pulmonary function tests

→

Psychiatric/Emotional Factors

- Symptom review based on the Survivorship Anxiety and Depression screening recommendations (See SANXDE-1 though SANXDE-5); evaluate for anticipation/fear of recurrence in the setting of:
  - Active surveillance by oncology team
  - New symptoms or findings suggestive of recurrence
  - Distress with body image
  - Transition periods:
    - Less frequent visits to oncologist due to treatment completion
    - Progression/recurrence
    - Awaiting treatment
    - Change in treatment modality
    - Treatment failure
    - Termination of treatment due to absence of available treatment options
    - End-of-life care

→

Social/External Factors

- Environmental stressors and non-cancer-related factors:
  - Social isolation, living alone
  - Family and caregiver conflicts
  - Financial problems and limited insurance coverage
  - Employment concerns
    - Discrimination in the work-place because of cancer diagnosis
    - Fear of losing health benefits and steady income
  - Limited access to medical care
  - Caregiver responsibilities
  - Younger age, survivors of childhood cancers, lack of peers
  - History of abuse (emotional, physical, sexual)

→ Management and Treatment (See SANXDE-7)

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ANXIETY/DEPRESSION: MANAGEMENT AND TREATMENT

NONPHARMACOLOGIC INTERVENTIONS

- Address treatable contributing factors
  - Pain, sleep disturbance, fatigue, toxic-metabolic/endocrine/other medical comorbidities, substance abuse
- Provide reassurance that symptoms of anxiety and depression are common problems among cancer survivors and that these symptoms can be treated
- Provide education to patient and family
- Encourage routine exercise
- Chaplaincy (ie, guilt, existential angst)
- Social work for involved, complicated social factors
- Therapy (social work, psychologist, psychiatrist, licensed therapist):
  - Supportive therapy and cognitive behavioral therapy (CBT) are both effective modalities
  - Normalization of patient's experience is an important component of support
  - Therapy should target management of anticipatory anxiety, adjustment issues following treatment, and somatic anxieties
- Refer to a psychiatrist in the following cases:
  - Extensive psychiatric history
  - Low-level suicidal ideation
  - Patient request
- Substance abuse treatment, withdrawal prevention counseling, monitoring

PHARMACOLOGIC INTERVENTIONS[h]

- First-line treatment:
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs):
    - Consider for concomitant pain, venlafaxine for hot flashes in setting of tamoxifen
  - Benzodiazepines (ie, clonazepam, lorazepam):
    - For acute anxiety relief, dose can be adjusted once SSRIs or SNRIs are fully effective and symptoms are partially or completely abated.

Monitor for potential side effects. Counsel patient that it may take up to 2 to 6 weeks at a therapeutic dose for SSRIs and SNRIs to take effect. Also counsel patients that symptoms of withdrawal may occur should any of the above-mentioned medications be abruptly discontinued.

- Consider referral to psychiatry for medication failure if no improvement on first-line treatment

[h] See Principles of Pharmacologic Interventions (SANXDE-B).

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SAFETY EVALUATION: ANXIETY/DEPRESSION

- Refer patient to the emergency room to determine need for psychiatric hospitalization in the following cases:
  - Suicide attempt
  - Suicidal ideation with a plan
  - Availability of weapons to a potentially dangerous person:
    - Individual who expresses violent impulses
    - Individual who wishes to harm self or others
  - Inability to care for oneself
  - High-risk patients when psychiatrist is not available

ACUTE (URGENT/EMERGENT) INTERVENTIONS

- Suicidal ideation, no plan →

Monitor closely
- Follow-up phone call to patient within a few days of the office visit
- Office visit within one week of expressed suicidal ideation
- Frequent visits until patient is more stable or psychiatric care in place
- Refer to psychiatrist if symptoms require pharmacologic intervention
- Refer to therapist

- Dangerousness; patients who are at risk for harming themselves or others:
  - Ask patient if they have access to firearms or other weapons →

Arrange to have weapons secured
- In addition to sending patient to emergency room by ambulance for a psychiatric evaluation, contact family members or close friend to arrange to remove weapons (patient should be informed of the plan)
- If the patient becomes agitated or threatening, involve other staff, keep door open, and call 911 (the safety of clinicians is essential to providing good care)

- Physical/Emotional Abuse →

Determine acuity, involve social work, mandatory reporting
- All clinicians are legally obligated to notify protective service agencies for vulnerable populations (ie, children, elderly, disabled)

- Substance Abuse/Dependence →

See Substance-Related Abuse/Disorder section in the NCCN Guidelines for Distress Management

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PRINCIPLES OF PHARMACOLOGIC INTERVENTIONS

Special Pharmacologic Considerations for Concomitant Problems:

- Substance abuse
  - Minimize use of benzodiazepines
  - Alternatives for sedation and acute anxiety are low-dose atypical neuroleptics (ie, olanzapine, quetiapine) or gabapentin
- Pain syndromes (eg, neuropathy) (See SPAIN-1)
  - Seratonin-norepinephrine reuptake inhibitors (SNRI)
  - Tricyclic antidepressants
    - Amitriptyline has sedating properties that may or may not be desirable
    - Nortriptyline and desipramine have the fewest side effects
- Menopausal symptoms (ie, hot flashes) (See SSFF-1)
  - Gabapentin (300-600 mg/day)
  - Venlafaxine extended release (37.5-75 mg/day)
- Fatigue (See SFAT-1)
  - Bupropion
- Insomnia (See SSD-1)
  - Mirtazapine, benzodiazepines, hypnotics (ie, zolpidem)

Caveats:

- Review side effects with patient, noting that some may be beneficial (sedation, arousal, or weight gain and appetite stimulation)
- Monitor QT interval on electrocardiogram at initiation and dose increases with neuroleptics
- Blood pressure should be monitored with venlafaxine and treated appropriately
- Refer to specialist if first-line treatment fails or if there are complicating factors such as chronic pain or substance abuse
- Consider avoiding psychotropics with fewer cytochrome P_{450} interactions in patients with complicated medical problems or high likelihood for recurrence

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COGNITIVE FUNCTION FOLLOWING CANCER TREATMENT

- **General Principles**
  - **Growing evidence supports the validity of the patient-reported experience of cognitive dysfunction associated with cancer treatment; there is modest correlation between patient reports of cognitive dysfunction and objective deficits with testing.**
  - **There is limited evidence to guide management of this condition, especially for cancers other than breast.**
  - **Patients benefit from validation of their symptom experience, a thorough evaluation of this concern and related issues, and education.**
  - **Imaging studies are generally not helpful, except when indicated by high-risk illness or focal neurologic deficits.**
  - **Patients who present with symptoms of cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment, especially depression.**
  - **Patients exposed to treatment known to cause cognitive dysfunction (ie, chemotherapy, brain irradiation) are likely to experience this condition.**
  - **Currently no effective brief screening tool for cancer-associated cognitive dysfunction has been identified. The Mini-Mental State Examination (MMSE®)[a] and similar screening tools lack adequate sensitivity for subtle decline in cognitive performance.**

[a]Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

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COGNITIVE FUNCTION ASSESSMENT

Focused history:
- Focal neurologic deficits
- High risk or known metastatic disease/brain primary
- Onset, temporality
- Age as risk factor for developing cognitive deficiency
- Trajectory over time
- Cancer treatment history, exposure to CNS radiation, intrathecal chemotherapy
- Prescription medications/over-the-counter medications and supplements
- Education attainment
- Nature of impairments per patient; clarifying questions may include[b]
  - Do you have difficulty paying attention? Multitasking?
  - Do you frequently leave tasks incomplete?
  - Do you have difficulty finding words?
  - Do you have difficulty remembering things?
  - Do you need to use more prompts like notes or reminders than you used to?
  - Does it take you longer to think through problems; does your thinking seem slower?
  - Do you have difficulty turning left across traffic?
  - Do you notice an impact on functional performance? Job performance?

Assessment of contributing factors:
- Medications/side effects
- Hormone status/menopause
- Emotional distress
  - Depression/anxiety (See SANXDE-1 and NCCN Guidelines for Distress Management)
- Symptom burden
  - Pain (See SPAIN-1)
  - Fatigue (See SFAT-1)
  - Sleep disturbance (See SSD-1)
- Comorbidities
- Use of alcohol and other agents that alter cognition

SPECIALIZED EVALUATION
- Imaging
- Neuropsychologic evaluation

→ See Cancer-associated Cognitive Dysfunction Interventions (SCF-3)

[b] Consider referral for specialized evaluation (neuropsychologic testing) if 2 or more questions prompt positive answers. Consideration of age, underlying neurologic impairment, and whether level of cognitive function is troubling to patient should inform decision.

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CANCER-ASSOCIATED COGNITIVE DYSFUNCTION INTERVENTIONS

Patient/Family Education and Counseling
- Validation of experience of cognitive dysfunction associated with cancer diagnosis and treatment
- Reassurance that cancer-associated cognitive dysfunction is not a progressive neurologic disorder like progressive dementias
- Support self-management and coping strategies

→

General Strategies for Management of Cancer-Associated Cognitive Dysfunction
- Teach enhanced organizational strategies (ie, use memory aids like notebooks and planners, keeping items in the same place, using reminder notes)
- Instruct patient to avoid multitasking and minimize distractions, especially at work
- Provide information about relaxation or stress management skills for daily use
- Provide assistance for sleep disturbance (See SSD-1) and fatigue (See SFAT-1)
- Recommend routine exercise
- Limit use of alcohol and other agents that alter cognition
- For older adults also see the cognitive function section of the NCCN Guidelines for Senior Adult Oncology (SAO-E)

→ See Specific Interventions (SCF-4)

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CANCER-ASSOCIATED COGNITIVE DYSFUNCTION SPECIFIC INTERVENTIONS

FIRST-LINE INTERVENTIONS

- **Neuropsychological evaluation and recommendations**[c]
- **Occupational therapy**[d]
- **Optimize management of:**
  - **Depression or emotional distress (See appropriate survivorship guidelines or NCCN Guidelines for Distress Management)**
  - **Sleep disturbance (See SSD-1)**
  - **Fatigue (See SFAT-1)**
  - **Contributing symptoms such as pain (See SPAIN-1)**
  - **Medical comorbidities**

SECOND-LINE INTERVENTIONS

→ **Consider use of psychostimulants (methylphenidate or modafinil)**

[c]Neuropsychological evaluation and intervention may be helpful when individuals perceive cognitive impairment in a non-specific way and clarity is needed about the nature of impairments to guide rehabilitative efforts. Neuropsychological evaluation itself can be therapeutic and validating. Evaluation may also be necessary if an individual is pursuing disability benefits and cognitive impairment is a contributing factor to work limitation.

[d]Occupational therapy strategies focus on improvement of cognitive functioning and may be most effective for an individual who notes the impact of specific functional limitations (ie, word finding, comprehension or task completion, quality-of-life or role expectations).

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DEFINITION OF CANCER-RELATED FATIGUE

- **Cancer-related fatigue is a distressing persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.**

CONSIDERATIONS FOR FATIGUE IN CANCER SURVIVORS

- **Fatigue is a common complaint in individuals undergoing cancer therapy and can be a persistent problem for some cancer survivors in the months and years after cancer diagnosis.**
  - **Receipt of chemotherapy and radiation are both pre-disposing factors for cancer-related fatigue, but it can be seen in some patients who are treated with surgery alone.**
  - **The time-course of fatigue is unique to the survivor and his or her treatment plan, but some general principles apply: Mild to moderate fatigue is common in cancer survivors who undergo chemotherapy and/or radiation; mild to moderate fatigue lasting up to one year can occur in a proportion of cancer survivors.**
  - **Fatigue that initially presents months after the completion of adjuvant therapy or fatigue that worsens over this period warrants additional evaluation.**

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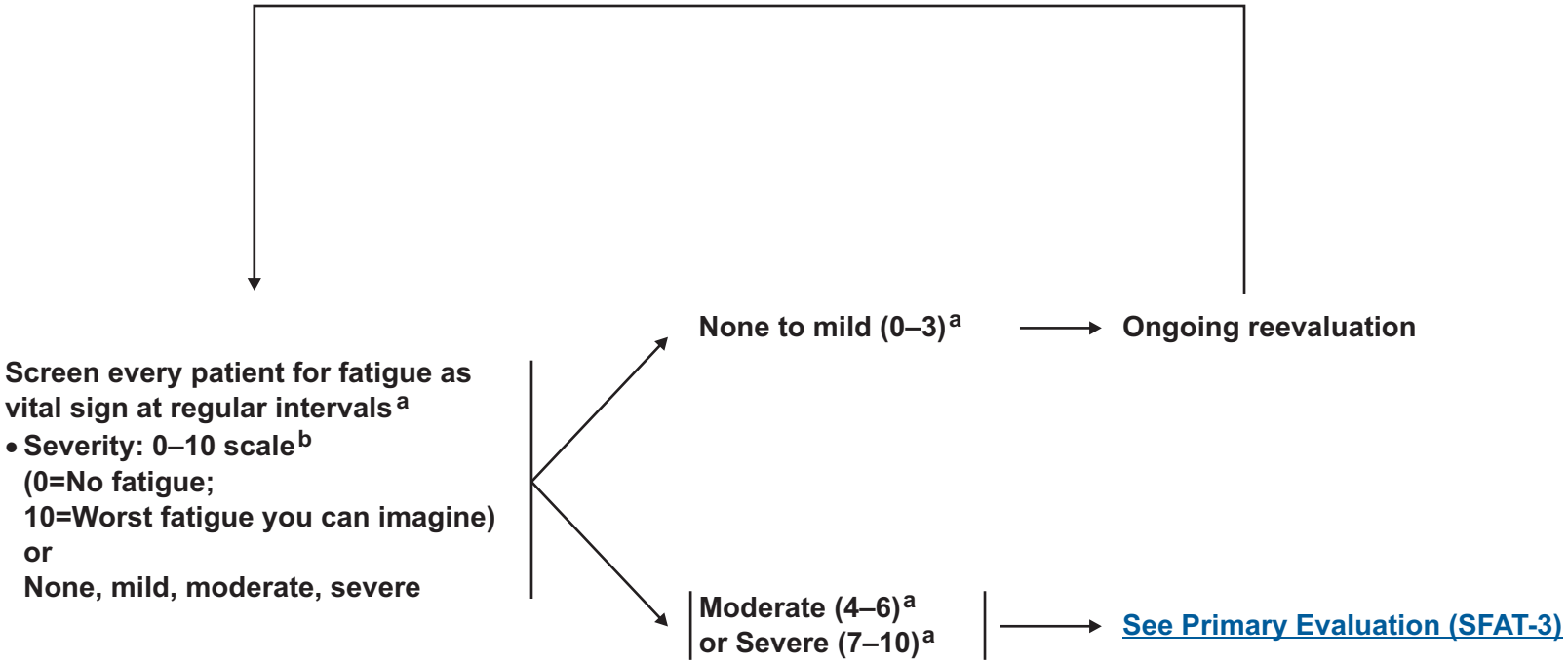
SCREENING



[a] Recommended screen and re-evaluation: "How would you rate your fatigue on a scale of 0–10 over the past 7 days?"

[b] Butt Z, Wagner LI, Beaumont JL, et al. Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. J Pain Symptom Manage 2008;35:20-30.

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PRIMARY EVALUATION FATIGUE SCORE: MODERATE OR SEVERE (4–10)

EVALUATION

History and Physical (H&P):

- Focused fatigue history
  - Onset, pattern, duration
  - Change over time
  - Associated or alleviating factors
  - Interference with function
- Evaluate disease status
  - Evaluate risk of recurrence based on stage, pathologic factors, and treatment history
  - Perform review of systems to determine if other symptoms substantiate suspicion for recurrence
- Assessment of treatable contributing factors:
  - Comorbidities
    - Alcohol/substance abuse
    - Cardiac dysfunction
    - Endocrine dysfunction (eg, hypothyroidism, hypogonadism, adrenal insufficiency)
    - Pulmonary dysfunction
    - Renal dysfunction
    - Anemia
    - Arthritis
  - Medications (eg, sleep aids, pain medications, or antiemetics)
  - Emotional distress- screen for anxiety and depression
  - Sleep disturbance (eg, insomnia, sleep apnea, vasomotor symptoms, restless leg syndrome) (See SSD-1)
  - Pain
  - Nutritional issues
    - Weight/caloric intake changes
  - Deconditioning/loss of muscle mass

→

Laboratory evaluation:

- Consider performing laboratory evaluation based on presence of other symptoms, onset, and severity of fatigue
  - CBC with differential
    - Compare end-of-treatment hemoglobin/hematocrit with current values
    - Assess other cell lines (WBC and platelets)
  - Comprehensive metabolic panel
    - Assess electrolytes
    - Assess hepatic and renal function
  - Endocrinologic evaluation
    - TSH in patients who have received prior head/neck, torso, or breast radiation
    - Consider more comprehensive evaluation or referral to specialist if other symptoms present
    - Cortical stimulation test, if history of prolonged steroid use

→

Imaging:

- Consider radiologic assessment only if high risk of disease recurrence OR if accompanying signs and symptoms suggest presence of metastatic disease
- Consider ECHO or MUGA for patients treated with an anthracycline, trastuzumab, bevacizumab, or other VEGF- or HER2-targeted therapy
- Chest x-ray and oxygen saturation testing for pulmonary complaints

→ **See Treatment of Contributing Factors (SFAT-4)**

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TREATMENT OF CONTRIBUTING FACTORS

- **Treat contributing factors:**
  - **Medications/side effects**
  - **Pain** (See SPAIN-1)
  - **Emotional distress**
    See (SANXDE-1) and NCCN Guidelines for Distress Management
  - **Anemia**
    - **Treat iron, B_{12}, folate deficiency, if present**
    - **Consider referral/further evaluation for anemia or cytopenias**
  - **Sleep disturbance** (See SSD-1)
  - **Nutritional deficit/imbalance**
  - **Comorbidities**

→ See Interventions for Cancer Survivors (SFAT-5)

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INTERVENTIONS FOR CANCER SURVIVORS

Patient/Family Education and Counseling

Provide information about patterns of fatigue during and after treatment
- Self-monitoring of fatigue levels
- Energy conservation
  - Set priorities
  - Pace
  - Schedule activities at times of peak energy

→

Physical Activity

- Maintain adequate levels of physical activity (category 1) (See SPA-1 and SPA-4)
- Survivors at higher risk of injury (eg, those living with neuropathy, cardiomyopathy, lymphedema, or other long-term effects of therapy or other comorbidities) should be referred to a physical therapist or exercise specialist
- Make use of local resources to help patients increase exercise
  - Exercise classes at cancer centers
  - Community programs focused on cancer survivors
  - Exercise professional certified by the American College of Sports Medicine
  - For patients with fatigue interfering with function, consider referral to a physical therapist or physiatrist

→

Other Behavioral Interventions[c]

- Psychosocial interventions (category 1)
  - Cognitive behavioral therapy[d]/Behavioral therapy (category 1)
  - Psycho-educational therapies/Educational therapies (category 1)
  - Supportive expressive therapies (category 1)[e]
- Nutrition consultation
- Cognitive behavioral therapy[d] for sleep (category 1) (See SSD-1)
  - Stimulus control
  - Sleep restriction
  - Sleep hygiene

→

Pharmacologic[f]

Consider psychostimulants[g] (methylphenidate[h]) after ruling out other causes of fatigue and failure of other interventions

[c] Interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources.

[d] A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and facilitate psychological adjustment.

[e] Supportive expressive therapies (such as support groups, counseling, and journal writing) facilitate expression of emotion and foster support from one or more people.

[f] Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients.

[g] Psychostimulants are at times used to treat cancer-related fatigue. A number of studies have evaluated their efficacy in the setting of active treatment and results have been mixed. There are extremely limited data regarding the use of these agents in the post-treatment setting.

[h] Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in cancer patients.

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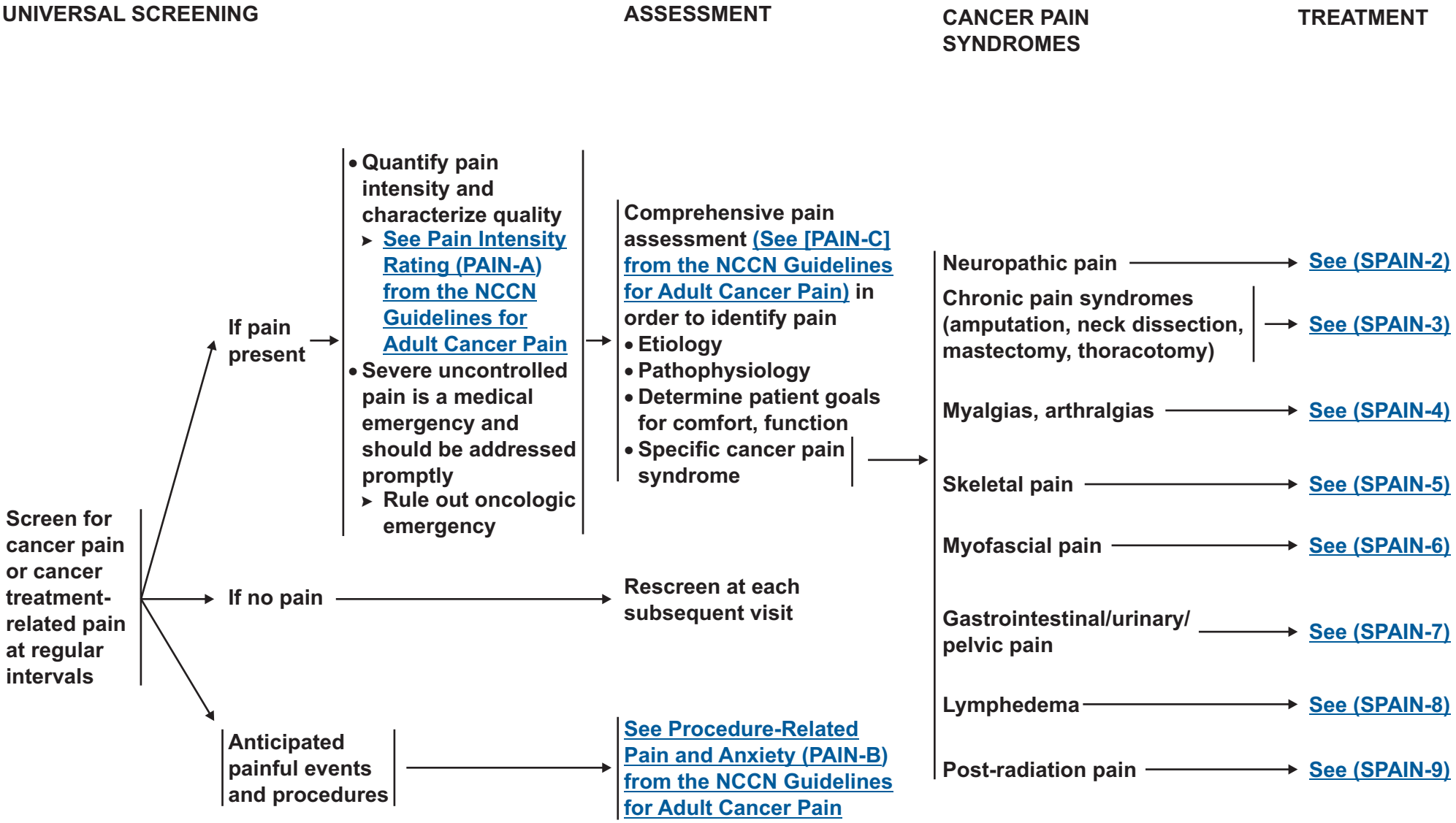

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CANCER PAIN SYNDROME	TREATMENT
Neuropathic pain →	• General measures: ▸ Adjuvant analgesics (See (PAIN-G) from the NCCN Guidelines for Adult Cancer Pain) ◊ Antidepressants ◊ Anticonvulsants ▸ Opioids[a] See (PAIN-3, PAIN-4, and PAIN-5) from the NCCN Guidelines for Adult Cancer Pain ▸ Cognitive behavioral therapy and psychosocial support (See (PAIN-H) from the NCCN Guidelines for Adult Cancer Pain) ◊ Consider hypnosis • For refractory pain, consider referral to pain management services, interventional specialist, physical therapy, physical medicine, and/or rehabilitation ▸ Local therapies ◊ Pharmacologic therapies ▪ Topical patches (lidoderm, capsaicin) ▪ Creams (ketamine and amitriptyline combined) ◊ Non-pharmacologic therapies ▪ Heat ▪ Ice ▪ Acupuncture ▪ Neurotomy with radiofrequency ablation ▪ Consider transcutaneous electrical nerve stimulation (TENS) unit ▪ Consider dorsal column stimulation

[a] See Principles of Opioid Use in Long-Term Survivors (SPAIN-A).

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CANCER PAIN SYNDROME	TREATMENT		TREATMENT
Chronic pain syndrome (amputation, neck dissection, mastectomy, thoracotomy) →	• General measures: ➤ Adjuvant analgesics See (PAIN-G) from the NCCN Guidelines for Adult Cancer Pain ➤ Psychosocial support and behavioral interventions See (PAIN-H) from the NCCN Guidelines for Adult Cancer Pain ➤ Opioids[a] See (PAIN-3, PAIN-4, and PAIN-5) from the NCCN Guidelines for Adult Cancer Pain • For refractory pain, consider referral to pain management services, interventional specialist, physical therapy, physical medicine, and/or rehabilitation for services such as: ➤ TENS unit ➤ Dorsal column stimulation ➤ Neurotomy with radiofrequency ablation	→ Specific chronic pain syndromes[b] →	• For post-amputation syndrome: ➤ Physical therapy for desensitization ➤ Cognitive therapy ➤ Upper extremities: Consider stellate ganglion block ➤ Lower extremities: Consider lumbar sympathetic block ➤ Neuromas: Consider phenol/alcohol block • For post-radical neck dissection syndrome: ➤ Physical therapy for stretching, range of motion ➤ Myofascial release ➤ Soft tissue massage ➤ Trigger point injections ➤ Possible botulinum toxin injection • For post-mastectomy or post-thoracotomy syndrome: ➤ Intercostal nerve block ➤ TENS unit

[a] See Principles of Opioid Use in Long-Term Survivors (SPAIN-A).
[b] There are other postoperative pain syndromes and many treatment measures can be used across syndromes. Also consider referral to appropriate specialist.

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CANCER PAIN SYNDROME	TREATMENT
Myalgias, Arthralgias	• Nonpharmacologic ► Physical activity ► Physical therapy ► Heat (paraffin wax, hot pack) ► Cold pack ► Aquatic therapy ► Ultrasonic stimulation[c] ► Massage ► Acupuncture • Pharmacologic ► Nonsteroidal anti-inflammatory drugs (NSAIDs) ► Muscle relaxants ► Anti-epileptic drugs (gabapentin, pregabalin) ► Serotonin-norepinephrine reuptake inhibitors (SNRIs) ► Tricyclic antidepressants (TCAs) • Consider referral to pain management services, interventional specialist, physical therapy, physical medicine, and/or rehabilitation

[c]Ultrasonic stimulation is a type of heat treatment that can penetrate directly to the bone and should be used with caution. It is not recommended for patients with multiple myeloma or bone metastases.

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CANCER PAIN SYNDROME	TREATMENT
Skeletal pain[d]	• For vertebral compression: ➤ General measures: ◊ Vitamin D/bisphosphonates ◊ NSAIDs ◊ Muscle relaxants ◊ Consider vertebral augmentation (vertebroplasty, kyphoplasty) ➤ Consider referral to pain management services, interventional specialist, physical therapy, physical medicine, and/or rehabilitation ➤ For acute vertebral compression: ◊ Opioids[a] ◊ Bracing (thoracolumbar sacral orthosis [TLSO], Jewett brace) ◊ Limited bedrest ◊ Weight-bearing exercises when pain improves ◊ Physical therapy ➤ For chronic vertebral compression: ◊ Weight-bearing exercises ◊ Physical therapy – thoracic and lumbar stabilization exercises • For avascular necrosis: ➤ Physical therapy – based on weight-bearing and range-of-motion restrictions ➤ Opioids[a] ➤ Muscle relaxants if myofascial component • For osteonecrosis of the jaw: ➤ Referral to oral surgeon ➤ Anti-convulsants ➤ SNRIs ➤ Opioids

[a] See Principles of Opioid Use in Long-Term Survivors (SPAIN-A).
[d] For skeletal metastases and/or bone pain, See (PAIN-D) from the NCCN Guidelines for Adult Cancer Pain.

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CANCER PAIN SYNDROME	TREATMENT
Myofascial pain →	• Consider referral to pain management services, interventional specialist, physical therapy, physical medicine, and/or rehabilitation for services such as: ► Trigger point injections ► Epidural steroid injections ► Radiofrequency ablation ► Dorsal column stimulation for intractable cases • Nonpharmacologic ► Physical therapy ► Range-of-motion exercises ► Strengthening exercises ► Soft tissue/myofascial release massage ► Ultrasonic stimulation[c] ► Acupuncture or acupressure • Pharmacologic ► Topical ointments (ketamine) and patches (lidocaine, capsaicin) ► NSAIDs ► Anti-epileptic drugs ► SNRIs • For muscle cramps, spasms ► Check electrolytes, calcium, magnesium levels, hydration status ► Massage ► Physical activity ► Physical therapy ► NSAIDs

[c] Ultrasonic stimulation is a type of heat treatment that can penetrate directly to the bone and should be used with caution. It is not recommended for patients with multiple myeloma or bone metastases.

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CANCER PAIN SYNDROME	TREATMENT
Gastrointestinal/urinary/pelvic pain →	• For gastrointestinal pain: ➤ Consider referral to gastroenterologist • For chronic pelvic pain: ➤ Consider referral to urologist or gynecologist ➤ Consider physical therapy for pelvic floor exercises ➤ Proper hydration ➤ Bowel regimen ➤ Dorsal column stimulation for chronic cystitis and chronic pelvic pai • For dyspareunia: ➤ See (SSFF-2) ➤ Consider referral to gynecologist or sexual health specialist • Consider referral to pain management services, interventional specialist, physical therapy, physical medicine, and/or rehabilitation

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CANCER PAIN SYNDROME	TREATMENT

Lymphedema	• Referral to lymphedema specialist, if available
	• Compression garments
	  ➤ Review fit and age of garments
	  ➤ Review use of garments
	  ➤ Ask about weight changes
	• Progressive resistance training with compression garments
	• Physical therapy with range of motion
	• Manual lymphatic drainage

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CANCER PAIN SYNDROME	TREATMENT
Post-radiation pain • Pain may be acute or appear months after radiation • Radiation may lead to scarring, adhesions, or fibrosis ➤ Differentiate fibrosis from recurrent tumor • Radiation to a localized area of the body may cause a chronic pain syndrome in that area	→ • Treat according to specific cancer pain syndrome guidelines, if appropriate (See SPAIN-1 for list of cancer pain syndromes) • Physical therapy • Pain medication (non-opioid medications such as antiepileptics, NSAIDs) • Surgical lysis of adhesions may be indicated in extreme circumstances

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PRINCIPLES OF OPIOID USE IN LONG-TERM SURVIVORS

- **Use the lowest opioid dose for the shortest period of time possible, if opioids are necessary**
- **Functionality may be a better endpoint for measuring outcomes, rather than numerical rating of pain**
- **Re-evaluate the effectiveness and necessity of opioids on a regular basis**
  - **If there is no improvement in function, or if opioid-induced hyperalgesia is suspected, recommend gradual tapering of opioids to help avoid symptoms of withdrawal**
  - **Discussion of gradual tapering should be routine**
  - **Consider establishing pain treatment agreements (See PAIN-L of the NCCN Guidelines for Adult Cancer Pain)**
- **Address medical-related issues due to chronic or high-dose opioids**
  - **Endocrine/hypopituitary abnormalities**
    - **Testosterone deficiency**

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NCCN Guidelines Version 1.2015
Sexual Function (Female)

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DIAGNOSTIC EVALUATION

- Ask about sexual function at regular intervals
- Use the Brief Sexual Symptom Checklist as a primary screening tool[a]
- Review present and past sexual activity and sexual concerns
- Discuss how cancer treatment has affected sexual functioning and intimacy
- Discuss treatment-associated infertility if indicated, with appropriate referrals[b]

No concerns regarding sexual function → Re-evaluate and discuss potential impact of treatment on sexual function at future visits

Concerns regarding sexual function →

- H&P
  - Sexual history (including prior problems, any history of abuse, prior STDs, safe sex practices)
  - Past medical, surgical, and obstetric histories (non-oncologic)
    - Identify traditional risk factors (eg, cardiovascular disease, diabetes mellitus, smoking, alcoholism, obesity, menopause)
  - Psychosocial history
    - Including relationship status/issues, body image concerns, and drug, alcohol, and tobacco use
    - Screen for psychosocial concerns (See [SANXDE-1] and NCCN Guidelines for Distress Management)
      - Depression
      - Anxiety
      - Relationship issues
  - Review oncologic history
    - Diagnosis/stage
    - Surgeries
    - Systemic treatment
    - Local RT
    - Endocrine therapy
  - Use of prescription and over-the-counter medications (particularly those known to effect sexual function)

→ See Additional Evaluation and Treatment (SSFF-2)
Appropriate referrals for:
- Psychotherapy
- Sexual/couples counseling
- Gynecologic care

[a] See Brief Sexual Symptom Checklist for Women (SSFF-A).

[b] For information regarding fertility preservation for cancer patients, see Loren AW, Mangu PB, Beck LN, et al. Fertility Preservation in Patients with Cancer: American Society of Clinical Oncology Guideline Update. J Clin Onc 2013: 31, 2500-2510. http://www.ncbi.nlm.nih.gov/pubmed/23715580

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NCCN Guidelines Version 1.2015
Sexual Function (Female)

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ADDITIONAL EVALUATION

- Evaluate for the following categories of female sexual dysfunctions:
  - Sexual desire and arousal disorder
  - Female orgasm disorder
  - Sexual pain disorder
- Discuss concerns related to specific cancer therapies
- If treatment-related menopause, assess symptoms and effects on sexual functioning
- Perform physical exam; perform or refer for gynecological exam to note points of tenderness, vaginal atrophy, and anatomic changes associated with cancer surgeries and treatments
- For more in-depth evaluation of sexual dysfunction, consider the Female Sexual Function Index (FSFI)[c] and/or the PROMIS® Sexual Function Instrument[d]

TREATMENT

- Guide treatment based on specific type of female sexual dysfunction:
  - Water-, oil-, or silicone-based lubricants
  - Vaginal moisturizers
  - Topical lidocaine
  - Vaginal dilators/vibrators
  - Relaxation techniques or exercises
    - Pelvic physical therapy helpful for anatomical changes and dyspareunia
  - Topical estrogen therapy if not contraindicated by tumor type (with education regarding risks)
    - Base the type of local estrogen on exam findings and patient preference (pills, vaginal rings, creams)
- Consider ospemifene for dyspareunia, if non-hormonally sensitive cancer
- Adjust medications that may affect sexual function
- Encourage ongoing partner communication
- Identify sources for psychosocial dysfunction with appropriate referrals for psychotherapy or sexual/couples counseling (multidisciplinary treatment plan)

POST-TREATMENT EVALUATION

Use the Brief Sexual Symptom Checklist[a]

- Concerns regarding sexual function improved or resolved → Re-evaluate and discuss potential impact of treatment on sexual function at future visits
- Ongoing concerns regarding sexual function → Repeat evaluation and treatment options, with appropriate referrals as indicated for:
  - Psychotherapy
  - Sexual/couples counseling
  - Gynecologic care

[a] See Brief Sexual Symptom Checklist for Women (SSFF-A).

[c] If Brief Sexual Symptom Checklist score is positive, consider using the Female Sexual Function Index (FSFI), which has been validated in cancer patients. Rosen R, Brown C, Heiman J, et al. The female sexual function index (FSFI): A multidimensional self-report instrument for the assessment of female sexual function. J Sex Mar Therapy 2000;26:191-208.

[d] Flynn KE, Reeve BB, Lin L, et al. Construct validity of the PROMIS® sexual function and satisfaction measures in patients with cancer. Health Qual Life Outcomes. 2013;11:40.

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BRIEF SEXUAL SYMPTOM CHECKLIST FOR WOMEN[1]

Please answer the following questions about your overall sexual function:

1. Are you satisfied with your sexual function?
__ Yes __No
If no, please continue.

2. How long have you been dissatisfied with your sexual function?

3a. The problem(s) with your sexual function is:
(mark one or more)
__1 Problem with little or no interest in sex
__2 Problem with decreased genital sensation (feeling)
__3 Problem with decreased vaginal lubrication (dryness)
__4 Problem reaching orgasm
__5 Problem with pain during sex
__6 Other:

3b. Which problem is most bothersome? (circle)
1 2 3 4 5 6

4. Would you like to talk about it with your doctor?
__Yes __No

[1]Reprinted with permission from Hatzichristou D, Rosen RC, Derogatis LR, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010;7:337-348. Review.

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

DIAGNOSTIC EVALUATION

- Ask about sexual function at regular intervals
- Review present and past level of sexual activity and discuss the potential impact of therapy. Discuss any sexual concerns and how cancer treatment has affected sexual functioning and intimacy
- Discuss treatment-associated infertility if indicated, with appropriate urologic (male infertility) referrals
- Laboratory tests:
  - HgbA1C, testosterone,[a] creatinine, cholesterol
- Consider questionnaire as a primary screening tool for erectile dysfunction (ED) (eg, Sexual Health Inventory for Men [SHIM])[b]

No concerns for sexual dysfunction → **Re-evaluate at subsequent visits/post therapy**

Concerns for sexual function →

- H&P
  - Sexual history (including prior problems)
  - Past medical and surgical histories
    - Identify traditional risk factors (eg, cardiovascular disease,[c] diabetes mellitus, smoking, alcoholism, obesity)
  - Psychosocial history
    - Including relationship status/issues, drug and alcohol use
    - Screen for psychosocial concerns (See [SANXDE-1] and NCCN Guidelines for Distress Management)
      - Depression
      - Anxiety
      - Relationship issues
  - Oncologic history
    - Diagnosis/stage
    - Surgeries
    - Systemic treatment
    - Local RT
  - Use of prescription and over-the-counter medications (especially hormone therapy or opiods)
  - Focused physical exam:
    - Chest (assess for gynecomastia)
    - Abdomen
    - Genitourinary exam (phallus, scrotum/testicles, cord structures)
    - Secondary sexual characteristics
    - Lower extremity pulses

→ See Initial Management (SSFM-2)

[a] Special consideration should be given to those men with androgen ablative therapy where testosterone replacement is ill-advised (ie, patient with advanced prostate cancer undergoing combination radiation/LHRH antagonist).

[b] See Sexual Health Inventory for Men (SHIM) (SSFM-A).

[c] The cardiovascular risk of all men with erectile dysfunction, especially those with cardiovascular disease, should be estimated. Sexual activity is equivalent to walking 1 mile in 20 minutes on a flat surface or to climbing 2 flights of stairs in 20 seconds. Patients with high risk should be referred to a cardiologist. (Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc 2012;87:766-778).

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INITIAL MANAGEMENT

- **Recommend modifying risk factors for ED:**
  - **Lifestyle modifications to improve vascular function such as smoking cessation, maintaining ideal body weight and engaging in regular exercise, and avoiding excess alcohol consumption**
- **Identify sources for psychosocial dysfunction with appropriate referrals for psychotherapy or sexual/couples counseling**
- **Consider the following therapies for ED:[d]**
  - **Oral phosphodiesterase type 5 (PDE5i) inhibitors as first-line therapy unless contraindicated (eg, patients taking oral nitrates)**
    - **Monitoring should include a periodic follow-up of efficacy, side effects, and any significant change in health status**
    - **An adequate trial of PDE5i should be defined as at least 5 separate occasions at the maximum dose before reporting it as non-effective unless the reason for fewer trials is an unacceptable side effect**

→ **Second trial of PDE5i (ie, a different PDE5i)[e]** →

SECOND TIER MANAGEMENT

- **Repeat evaluation and treatment options, with appropriate referrals for psychotherapy, sexual counseling as indicated**
- **If second trial of PDE5i fails, consider the following therapies for ED with referral to a urologist:**
  - **Intra-urethral alprostadil suppositories**
  - **Intracavernous vasoactive drug injection therapy**
  - **Vacuum constriction devices (VCD)**
  - **Penile prosthesis implantation (if the above methods fail)**

[d] The management of ED should be applied in a stepwise fashion with increasing invasiveness and risk balanced against efficacy. The patient and, when possible, his partner should be informed of the relevant treatment options and their associated risks and benefits.

[e] Prior to proceeding to other therapies, those with a failure of first-line PDE5i therapy should be evaluated to determine whether the trial of PDE5i was adequate. Consider switching the dose before moving to second-line therapies.

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SEXUAL HEALTH INVENTORY FOR MEN (SHIM)[1]

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that best describes your own situation.

Please be sure that you select one and only one response for each question.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence you could get and keep an erection?		Very Low	Low	Moderate	High	Very High
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)	No Sexual Activity	Almost Never or Never	A Few Times (Much Less Than Half The Time)	Sometimes (About Half the Time)	Most Times (Much More Than, Half The Time)	Almost Always or Always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (Much Less Than Half The Time)	Sometimes (About Half the Time)	Most Times (Much More Than, Half The Time)	Almost Always or Always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (Much Less Than Half The Time)	Sometimes (About Half the Time)	Most Times (Much More Than, Half The Time)	Almost Always or Always
	0	1	2	3	4	5

PROVIDER KEY: Add the numbers corresponding to questions 1-5. **TOTAL: _____**

The SHIM further classifies ED severity with the following breakpoints: 1-7: Severe ED 8-11: Moderate ED 12-16: Mild to Moderate ED 17-21 Mild ED

[1] Reproduced and modified with permission from Cappelleri JC, Rosen RC. The Sexual Health Inventory for Men (SHIM): a 5-year review of research and clinical experience. Int J Impot Res 2005;17:307-319.

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NCCN Guidelines Version 1.2015
Sleep Disorders

SCREENING

Screening/assessment questions to be asked at regular intervals, especially when there is a change in clinical status or treatment:

- **Insomnia**
  - **Do you have difficulty falling or staying asleep?**
  - **How long does it take to fall asleep?**
  - **How many times do you wake up every night?**
  - **How long have you had difficulty falling or staying asleep?**
- **Excessive sleepiness**
  - **Do you fall asleep while reading, watching television, talking to friends, or driving?**
- **Obstructive sleep apnea[a]**
  - **Do you snore, gasp for breath, or stop breathing during sleep?**
- **Restless legs syndrome (RLS)[a]**
  - **Do you have the urge to move the legs, usually accompanied by an uncomfortable, deep-seated sensation that is brought on by rest?**
- **Parasomnias[a,b]**
  - **Do you sleep walk, wake up screaming, or have violent movements during sleep?**

No concerns for sleep disorder/disturbance → **Re-evaluate at subsequent visits/post therapy**

Concerns for sleep disorder/ disturbance →

H&P

- **Assessment of treatable contributing factors:**
  - **Comorbidities**
    - **Alcohol and/or substance abuse**
    - **Obesity**
    - **Cardiac dysfunction**
    - **Endocrine dysfunction (eg, hypothyroidism)**
    - **Anemia**
    - **Emotional distress: screen for anxiety and depression (See SANXDE-1 and NCCN Guidelines for Distress Management)**
    - **Neurologic disorders**
    - **Psychiatric disorders**
  - **Medications (consider persistent use of sleep aids, pain medications, antiemetics, stimulants, sedative/hypnotics, over-the-counter sleep aids, or antihistamines)**
  - **Review history of chemotherapy**
  - **Pain (See SPAIN-1)**
  - **Fatigue (See SFAT-1)**
  - **Shift work**
  - **Current coping strategies (relaxation techniques, meditation, etc.)**

- **Sleep disturbance and/or excessive sleepiness**
  - **Narcolepsy and other hypersomnias**
  - **Obstructive sleep apnea[a]**
  - **Restless legs syndrome (RLS)[a,c]**
  - **Circadian rhythm sleep disorders[a,b]**
  - **Parasomnias[a,b]**

  → **See SSD-2**

- **Insomnia symptoms (difficulty falling asleep and/or maintaining sleep):**
  - **Duration >4 weeks**
  - **Occurring at least 3 times per week**

  → **See SSD-4**

[a]Note that obstructive sleep apnea, restless legs syndrome, circadian rhythm sleep disorders, and parasomnia may also present with symptoms of insomnia.
[b]For circadian rhythm sleep disorders and parasomnias, refer to a sleep specialist.
[c]Restless leg syndrome is also known as Willis-Ekbom disease.

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SYMPTOM	ASSESSMENT[d]	TESTING	DIAGNOSIS[d]	TREATMENT
Sleep disturbance and/or Excessive sleepiness	Associated with insufficient sleep time		Insufficient sleep syndrome	• Increase sleep time • Sleep hygiene education[i]
	Associated with observed apneas, snoring[e]	Polysomnography (PSG)[h]	Obstructive sleep apnea	Consider: • Continuous positive airway pressure (CPAP) • Surgery • Oral appliance • Weight loss • Exercise (See SPA-1) • Refer to sleep specialist
	Associated with uncomfortable sensation[f]	Ferritin level <45-50 ng per mL	Restless leg syndrome (RLS)[c,f]	• Dopamine agonists • Benzodiazepines (BZD) • Gabapentin (enacarbil) • Opioids[c] • Refer to sleep specialist
	Associated with prolonged wakefulness or awakenings			See SSD-3
	Associated with prolonged nocturnal sleep (ie, >9 hours for adults)			
	Associated with cataplexy,[g] frequent short naps, vivid dreams, disrupted sleep, or sleep paralysis			
	Excessive daytime sleepiness not associated with other symptoms			

[c] Restless leg syndrome is also known as Willis-Ekbom disease.
[d] For other less frequent syndromes, refer to sleep specialist.
[e] See STOP Questionnaire: A Tool to Screen Patients for Obstructive Sleep Apnea (SSD-A).
[f] See Essential Diagnostic Criteria for Restless Legs Syndrome (SSD-B).
[g] Cataplexy: Sudden loss of muscle tone. Typically triggered by strong emotions, such as laughter or anger. Cataplexy is the most specific diagnostic feature of narcolepsy.
[h] Sleep studies can be done as laboratory PSG or as home sleep study.
[i] See General Sleep Hygiene Measures (SSD-C).

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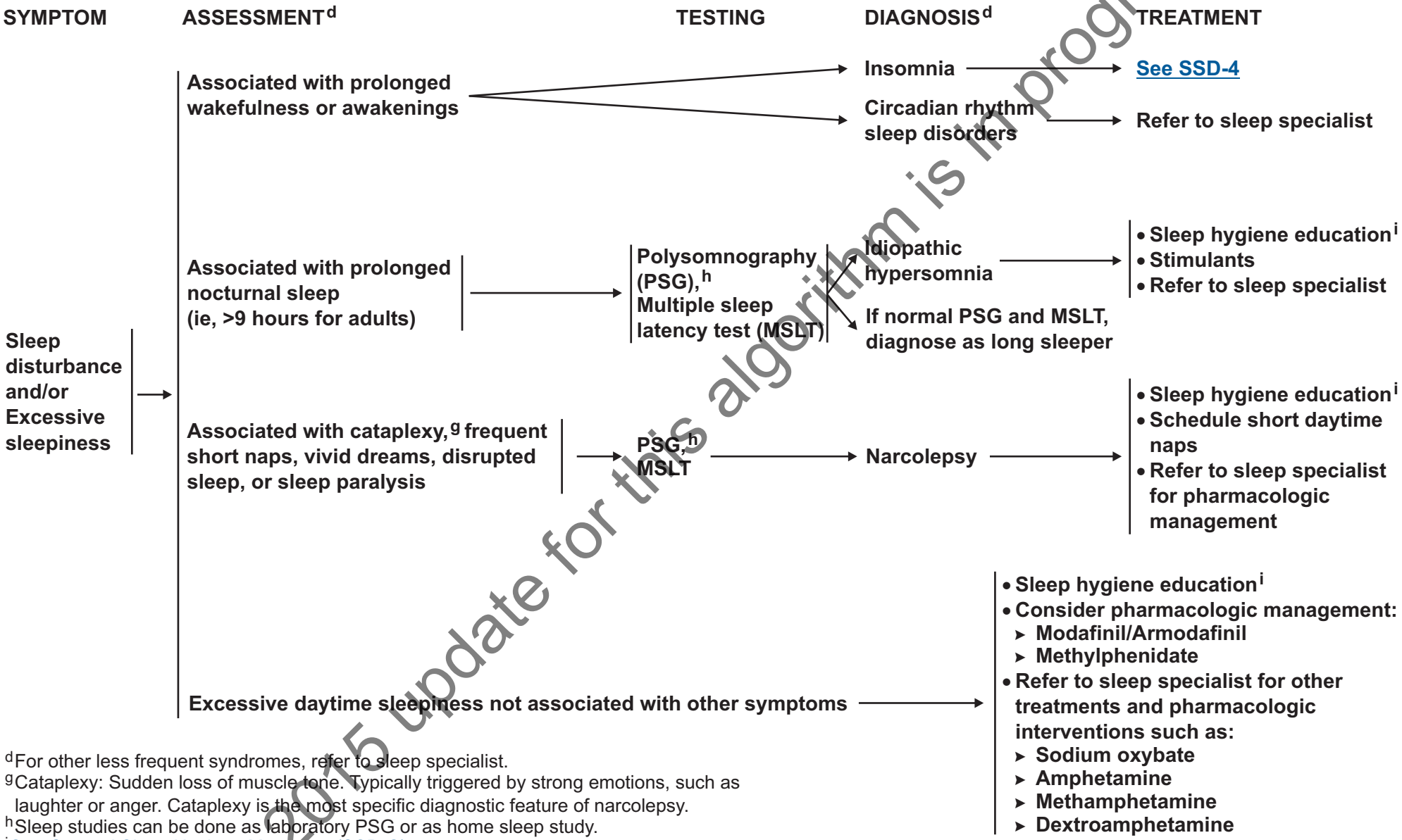

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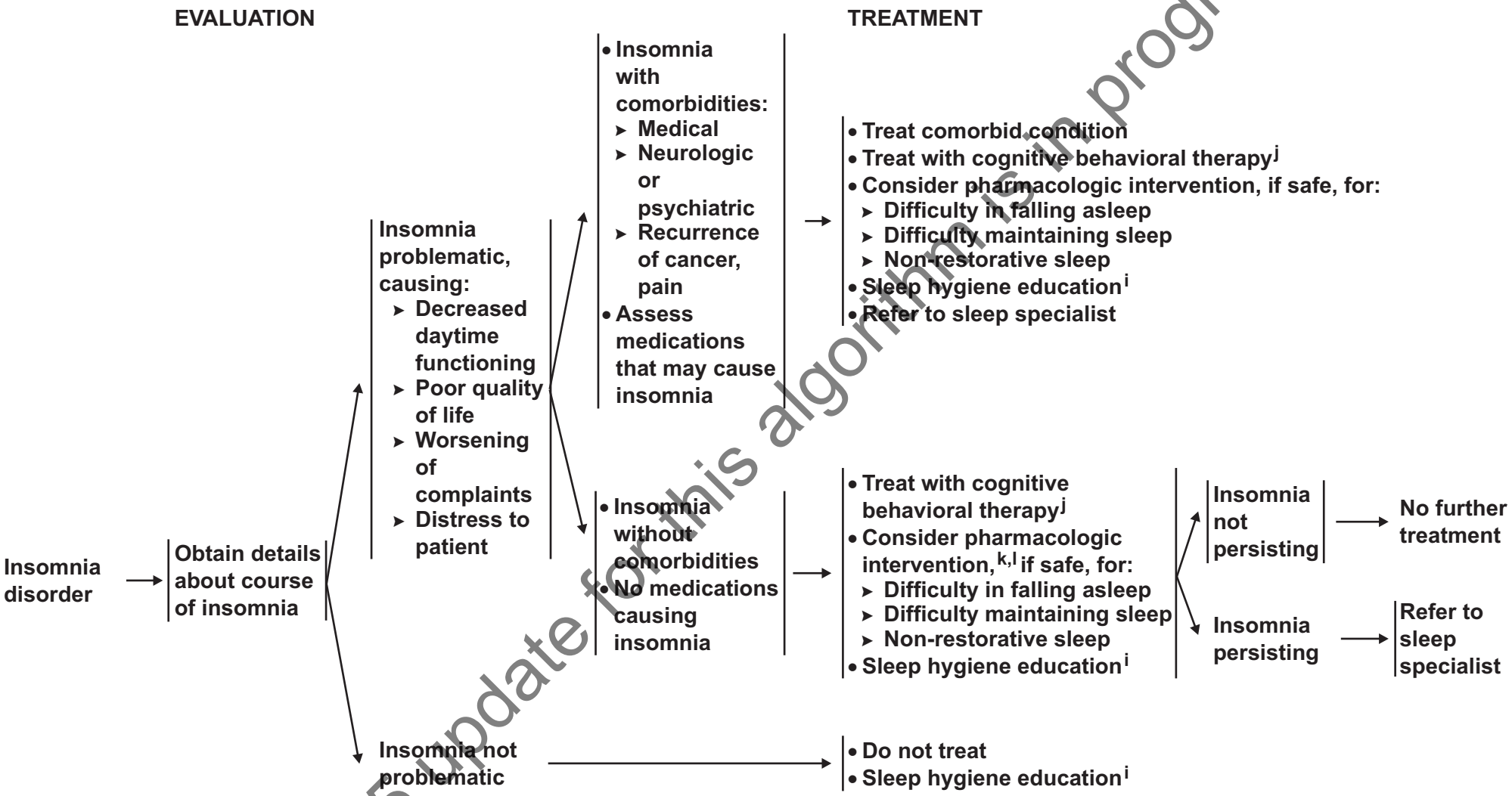

[i] See General Sleep Hygiene Measures (SSD-C).
[j] See Cognitive Behavioral Treatments (SSD-D).
[k] See Principles for Choosing an FDA-Approved Hypnotic (SSD-E).
[l] See Other Commonly Used Medications For Insomnia (SSD-F).

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STOP Questionnaire: A Tool to Screen Patients for Obstructive Sleep Apnea (OSA)[1, 2]

1. **Snoring**
   Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?
   Yes No

2. **Tired**
   Do you often feel tired, fatigued, or sleepy during daytime?
   Yes No

3. **Observed**
   Has anyone observed you stop breathing during your sleep?
   Yes No

4. **Blood pressure**
   Do you have or are you being treated for high blood pressure?
   Yes No

PROVIDER KEY
High risk of OSA: Answering yes to two or more questions
Low risk of OSA: Answering yes to less than two questions

[1]Reproduced and modified with permission from Chung, Yegneswaran, B, Liao, P, et al. STOP Questionnaire: A Tool to Screen Patients for Obstructive Sleep Apnea. Anesthesiology 2008;108:812-821.
[2]This screening tool and other similar tools are not diagnostic, but have been shown to be useful to assess risk for OSA.

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ESSENTIAL DIAGNOSTIC CRITERIA FOR RESTLESS LEGS SYNDROME[1]

- **An urge to move the legs usually accompanied by uncomfortable and unpleasant sensations in the legs, and sometimes the arms or other body parts.**
- **The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.**
- **The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching.**
- **The symptoms are more pronounced in the evening or night or may only occur in the evening or night.**

[1]Reproduced with permission from Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101-119.

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GENERAL SLEEP HYGIENE MEASURES[1,2,3]

- Regular exercise in the morning and/or afternoon
- Increase exposure to bright light during the day
- Avoid exposure to bright light during the night
- Avoid heavy meals or drinking within 3 hours of bed
- Avoid alcohol, caffeine, nicotine too close to bedtime
- Enhance sleep environment (dark, quiet room, comfortable temperature)
- Set aside a worry time
- Avoid looking at the clock

[1]National Heart, Lung, and Blood Institute Working Group on Insomnia. Insomnia: Assessment and Management in Primary Care. 1998. NIH Publication. 98-4088;
[2]Kupfer DJ and Reynolds CF. Management of insomnia. N Engl J Med. 1997;336:341-346
[3]Lippmann S, Mazour I, Shahab H. Insomnia: therapeutic approach. South Med J. 2001;94:866-873.

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COGNITIVE BEHAVIORAL TREATMENTS[1]

Strategy	Goal
Cognitive therapy	• Challenge patient's dysfunctional beliefs and misconceptions about sleep disturbances. • Promote positive thoughts.
Relaxation training	• Reduce physiologic and cognitive arousal at bedtime • Techniques include progressive muscular relaxation, transcendental meditation, yoga, biofeedback
Sleep restriction	• Improve sleep continuity by limiting time spent in bed and maintaining a regular sleep schedule
Stimulus control	• Associate the bed/bedroom as a place for sleep or sexual activity only

[1]Data from Bootzin RR and Perlis ML. Nonpharmacologic treatments of insomnia. J Clin Psychiatry 1992;53(suppl):37-41.

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PRINCIPLES FOR CHOOSING AN FDA-APPROVED HYPNOTIC:[1]

- **Does the patient have difficulty initiating or maintaining sleep?**
- **Does the patient have both sleep onset and sleep maintenance difficulty?**

AGENT	HELPS WITH SLEEP INITIATION	INCREASES TOTAL SLEEP TIME	INDICATED FOR SLEEP ONSET AND MAINTENANCE
Zolpidem	+	+	–
Zolpidem CR	+	+	+
Zaleplon	+	–	–
Eszopiclone	+	+	+
Ramelteon	+	+/-	–
Temazepam	+	+	+
Doxepin (3-6 mg)	–	+	+
Lorazepam	+	–	–

[1]Data from the Physicians' Desk Reference (ed 66). Montvale, NJ: PDR Network, LLC; 2012.

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OTHER COMMONLY USED MEDICATIONS FOR INSOMNIA[1]

This is a list of agents that do not have an FDA-approved indication for the treatment of insomnia and that do not have enough data to be recommended for routine use. They have none to limited efficacy or effectiveness data for the treatment of insomnia disorder.

Antidepressants[2]
- Trazodone
- Amitriptyline
- Trimipramine
- Mirtazapine
- Doxepin

Antihistamines[2]
- Diphenhydramine

Anti-epileptics[2]
- Gabapentin
- Tiagabine

Atypical antipsychotics[2]
- Quetiapine

Nutritional/Herbal supplements
- Melatonin
- Valerian

[1]From Neubauer, D. Evolution and Development of Insomnia Pharmacotherapies. J Clin Sleep Med. 2007 August 15; 3(5 Suppl): S11–S16. and Sleep; National Institutes of Health State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults; June 13-15, 2005; 1049-1057.
[2]Although they are commonly prescribed, antidepressants, antihistamines, anti-epileptics, and antipsychotics have significant risks and should be used with caution.

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Preventive Health

GENERAL PRINCIPLES OF HEALTHY LIFESTYLES

- All survivors should be encouraged to achieve and maintain a healthy lifestyle with attention to weight management (SNWM-2), physical activity (SPA-1), and healthy dietary habits (SNWM-1).
- Healthy lifestyle habits have been associated with improved overall health and quality of life. For some cancers, a healthy lifestyle has been associated with a reduced risk of recurrence and death.
- For a healthy lifestyle, all survivors should be encouraged to:
  - Achieve and maintain a healthy body weight throughout life (SNWM-2).
    - Pay attention to calories consumed versus calories expended via diet and exercise.
    - Achieve and maintain a normal body mass index (BMI) (SNWM-A).
    - Weigh oneself weekly to monitor weight gain/loss.
  - Engage in physical activity regularly (SPA-1)
    - Avoid inactivity; engage in general physical activity daily (eg, taking the stairs, parking in the back of parking lot).
    - Strive for at least 150 minutes of moderate or 75 minutes of vigorous activity per week, spread out over the course of the week.
  - Maintain a healthy diet high in fruits, vegetables, and whole grains and low in red and processed meats, sugars, and fats in order to promote weight control and avoid obesity. (SNWM-1).
  - Minimize alcohol intake.
    - Limit intake to one drink per day for a woman and two drinks per day for a man.[a]
  - Avoid tobacco products.
    - Attempt tobacco cessation if currently smoking or using smokeless tobacco.
  - Practice sun safety.
    - Utilize a sunscreen with an SPF of at least 30 that protects against UVA and UVB rays and is water resistant.
    - Apply sunscreen generously and reapply every two hours or after swimming/excessive sweating.
    - Consider using physical barriers whenever possible (ie, hats, shirts with sleeves, avoiding direct sun during peak hours.)
  - Follow up with primary care physician regularly.
    - Adhere to age-appropriate health screening, preventive measures (SIMIN-1), and cancer screening recommendations (See NCCN Guidelines for Detection, Prevention and Early Detection).
- Routine use of dietary supplements is not recommended for the purposes of cancer control (SSUP-1).
- Survivors should work with primary care to set incremental goals for diet, physical activity, and weight management.

[a]Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242-274. Available at: http://onlinelibrary.wiley.com/doi/10.3322/caac.21142/full

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GENERAL PRINCIPLES OF PHYSICAL ACTIVITY

- **Avoid inactivity; engage in general physical activity daily**
  - **Physical activity includes exercise, daily routine activities, and recreational activities**
- **Physical activity and exercise recommendations should be tailored to individual survivor's abilities and preferences**
- **General recommendations for cancer survivors:[a]**
  - **Overall volume of weekly activity should be at least 150 minutes of moderate-intensity[b] activity or 75 minutes of vigorous-intensity[b] activity or equivalent combination**
  - **Two to three sessions per week of strength training that include major muscle groups**
  - **Stretch major muscle groups on a routine basis**

[a] Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242-274. Available at: http://onlinelibrary.wiley.com/doi/10.3322/caac.21142/full and Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Medicine & Science in Sports & Exercise 2010;42:1409-1426. Available at: http://journals.lww.com/acsm-msse/Fulltext/2010/07000/American_College_of_Sports_Medicine_Roundtable_on.23.aspx

[b] Light exercise: No noticeable change in breathing pattern; Moderate exercise: Can talk, but not sing; Vigorous exercise: Can say a few words without stopping to catch a breath (See Examples of Exercise [SPA-B]).

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PHYSICAL ACTIVITY ASSESSMENT

Ask about prior and current participation in physical activity and assess level of current physical activity at regular intervals

→

Focused clinical evaluation
- Weight/BMI
- Blood pressure
- Functional status/performance status
- Assess baseline level of activity prior to diagnosis and current level of activity[c]
- Barriers to physical activity as assessed by survivor
  - Environmental (home, gym access, outdoor space)
  - Financial
  - Physical limits
  - Time/competing demands
  - Social support
  - Stress
- Review of systems
- Disease status
- Nutritional status

Assessment of treatable contributing factors
- Pain
- Fatigue
- Emotional distress
- Nutritional deficits/imbalance
- Medications

→

Assessment of comorbidities and treatment effects as appropriate:
- Cardiovascular disease (including cardiomyopathy)
- Pulmonary disease
- Arthritis/musculoskeletal issues
- Lymphedema
- Peripheral neuropathy
- Bone health/bone strength (including presence of bone metastases)
- Incontinence
- Presence of stoma or ostomy
- Fall risk assessment
- Need for assistive devices (cane, walker, brace, etc)
- History or presence of anemia/thrombocytopenia
- Steroid myopathy

→

Determine risk level for exercise-induced adverse events
(See SPA-3)

[c]Ask patient about duration, intensity, and frequency of activity. For example see Godin G and Shepard RJ. Godin Leisure-Time Exercise questionnaire. Medicine and Science in Sports and Exercise 1997; 29 June Supplement: S36-S38. (http://healthandfitnessjournalofcanada.com/index.php/html/article/viewFile/82/49)

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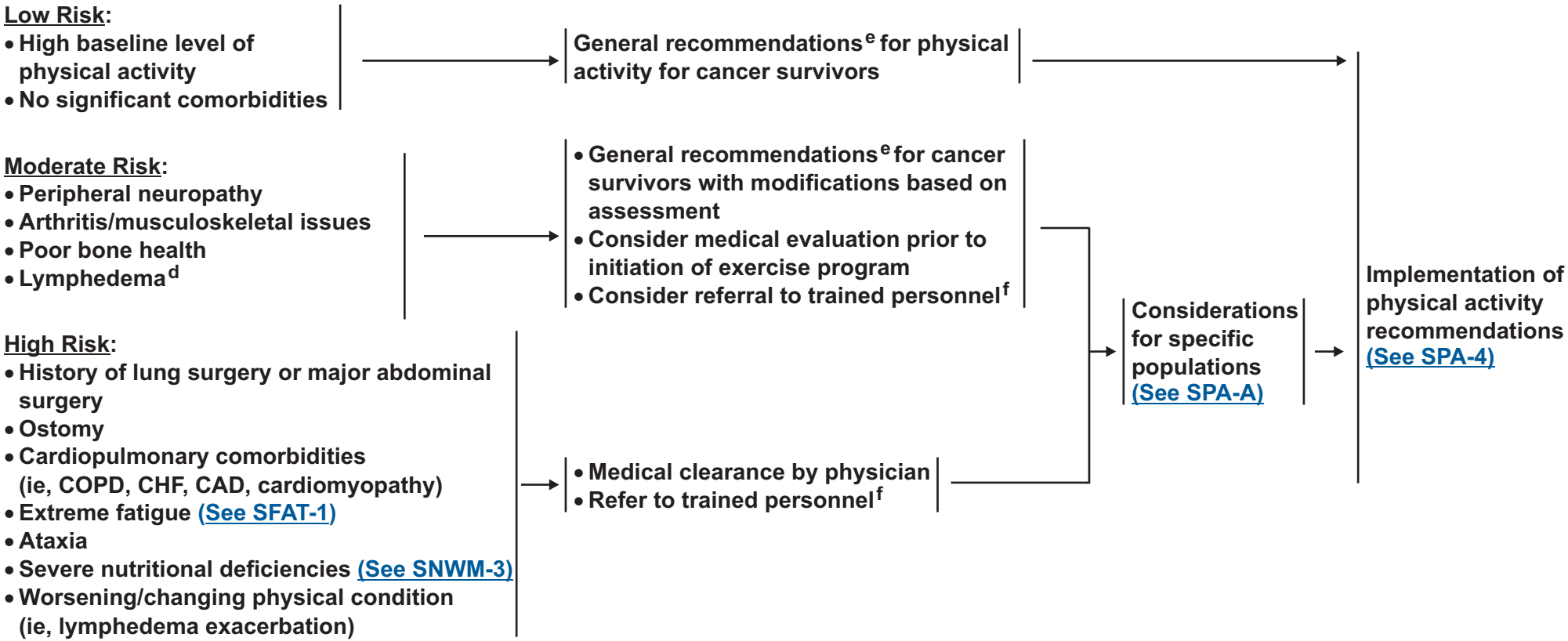
RISK ASSESSMENT FOR PHYSICAL ACTIVITY-INDUCED ADVERSE EVENTS



[d] Lymphedema patients are considered high-risk if performing resistance/strength training exercise of the affected limb. They are not considered high-risk if participating in cardiovascular/aerobic exercise or strength training of unaffected limbs. Patient education about the risk of lymphedema is recommended. Consider referral to lymphedema specialist for evaluation prior to starting physical activity program that involves strength or resistance training of the affected limb.

[e] See General Principles of Physical Activity (SPA-1).

[f] Trained personal can include physical therapists, certified trainers, cancer rehabilitation specialists, pulmonary or cardiac rehabilitation specialist, or exercise specialists. Specialized training in cancer exercise is available through the American College of Sports Medicine (ACSM) (http://www.acsm.org/get-certified). Patients should be encouraged to use an ACSM-certified trainer when available.

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IMPLEMENTATION OF RECOMMENDATIONS[g]

Meeting Guideline recommendations[e,h] →

- Periodic reassessment, positive reinforcement with review of benefits of exercise, and encouragement to maintain activity level[j]
- Discuss and review possible side effects of exercise (eg, pain)
- Continued reinforcement of guideline recommendations at follow-up visits
- If tolerating, consider variation, additional activity, or progression to:
  - Frequency: 4-6 days/week
  - Intensity: Light to vigorous[j]
  - Type: Varied aerobic, resistance prescription,[k] endurance
  - Time: 20-60 minutes/session

Current or prior exercise behavior:
- Frequency
- Intensity
- Type
- Time

Not meeting Guideline recommendations[e] and/or Moderate- to high-risk patients[i] (See SPA-3) →

- Survivors and providers should work together to develop incremental short- and long-term goals regarding physical activity participation. These may include incremental increases in time spent in physical activity or in intensity of activity.
- Suggested initial prescription:
  - Frequency: 1-3 days/week
  - Intensity: Light to moderate[j]
  - Type: Brisk walking and/or resistance prescription[k]
  - Time goal: 20 minutes/session

→ **If tolerating[j]** →

If tolerating[h] ↑

Progression:
- Frequency: Up to 5 days/week
- Intensity: Light to moderate[j]
- Type: Brisk walking and/or resistance prescription[k]
- Time: 20-60 minutes/session as tolerated

[e] See General Principles of Physical Activity (SPA-1).

[g] Reproduced and adapted as shown in Jones L, Eves ND, Pepperorn J. Pre-exercise screening and prescription guidelines for cancer patients. Lancet Oncol 2010;11:914-916 with permission from Metkus TS Jr, Baughman KL, Thompson PD, et al. Exercise prescription and primary prevention of cardiovascular disease. Circulation 2010;121:2601-2604.

[h] If tolerating minimum guideline recommendations, consider encouragement of variation within exercise program or physical activities.

[i] Moderate to high-risk patients may need additional evaluation before doing more rigorous activity.

[j] See Examples of Exercise, Strategies to Increase Physical Activity (SPA-B).

[k] See Guidance For Resistance Training Recommendations (SPA-C)

Note: All recommendations are category 2A unless otherwise indicated.
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CONSIDERATIONS FOR SPECIFIC POPULATIONS[1]

- **Lymphedema:**
  - Survivors with lymphedema should utilize compression garments when engaging in exercise
  - Work with trained exercise professional if considering weight training or resistance training
  - Undergo baseline and periodic evaluation for development or exacerbation of lymphedema
  - Initiate strength training exercise involving affected body part only if lymphedema stable:
    - No need for lymphedema therapy within past 3 months
    - No recent limb infections requiring antibiotics
    - No change in limb circumference >10%
    - No change in ability to perform activities of daily living
  - Resistance training/weight lifting: Gradually increase resistance by smallest increment possible with monitoring
  - Stop exercise and refer to lymphedema specialist if exacerbation of lymphedema occurs
  - Continued full use of the extremity and range-of-motion exercises are encouraged to maintain strength and range of motion even in the presence of lymphedema

- **Stem cell transplant:**
  - Initiate physical activity as tolerated, with clearance by transplant provider
  - Survivors with indwelling catheters should avoid swimming until catheter is removed.
  - Public gym use should not be discouraged because the benefits of exercise outweigh the risk of exposure

- **Ostomy:**
  - Empty ostomy bag before engaging in exercise
  - Weight lifting/resistance exercises should start with low resistance and progress slowly under the guidance of trained exercise professionals
  - Avoid contact sports and exercises that result in excessive intra-abdominal pressure
  - Infection precautions recommended

- **Peripheral neuropathy:**
  - Stability, balance, and gait should be assessed before engaging in exercise
  - Consider alternative aerobic exercise (stationary biking, water aerobics) rather than walking if neuropathy affects stability
  - Monitor discomfort in hands when using hand-held weights. Consider using dumbbells with soft/rubber coating, and/or wear padded gloves (eg, cycling gloves)

- **Poor bone health:**
  - Survivors with osteoporosis or bone metastases should have fracture risk and/or bone density assessed before initiation of exercise program as clinically indicated

[1]When possible, survivors in these populations should initiate exercise program under supervision by trained personnel. Trained personal can include physical therapists, certified trainers, cancer rehabilitation specialists, or exercise specialists. Specialized training in cancer exercise is available through the American College of Sports Medicine (ACSM) (http://www.acsm.org/get-certified). Patients should be encouraged to use an ACSM-certified trainer when available.

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EXAMPLES OF PHYSICAL ACTIVITY

Light Exercise[1]
(No noticeable change in breathing pattern)

- Leisurely biking at 5 miles/hour or less
- Activity-promoting video game
- Light housework (light sweeping, dusting)
- Bowling
- Playing catch
- Slow walking
- Garage work
- Child care
- Yoga
- Tai chi

Moderate Exercise[2]
(Can talk, but not sing)

- Ballroom/line dancing
- Biking on level ground or with few hills
- General gardening
- Baseball, softball, volleyball
- Doubles tennis
- Using a manual wheelchair
- Using hand cyclers (ergometers)
- Brisk walking
- Water aerobics
- Yoga

Vigorous Exercise[2]
(Can say a few words without stopping to catch a breath)

- Aerobic/Fast dancing
- Biking faster than 10 miles/hour
- Heavy gardening
- Hiking uphill
- Jumping rope
- Martial arts
- Race walking, jogging, running
- Running sports (basketball, hockey, soccer)
- Swimming (fast pace or laps)
- Singles tennis
- Stair climbing
- High intensity yoga

STRATEGIES TO INCREASE PHYSICAL ACTIVITY

- Physician and/or fitness expert recommendation
- Supervised exercise program or classes
- Telephone counseling
- Motivational counseling
- Evaluate readiness to change, importance of change, self-efficacy
- Cancer survivor-specific print materials (See SURV-B 2 of 2)
- Set short- and long-term goals

[1] From the National Heart, Lung, and Blood Institute (http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/phy_act.htm) and the Compendium of Physical Activities (https://sites.google.com/site/compendiumofphysicalactivities).

[2] Reproduced and adapted from U.S. Department of Health and Human Services. Be Active Your Way: A Fact Sheet for Adults. Washington, DC: U.S. Department of Health and Human Services; 2008. http://www.health.gov/PAGuidelines/factSheetAdults.aspx. Accessed February 22, 2013.

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GUIDANCE FOR RESISTANCE TRAINING RECOMMENDATIONS

- **Health benefits of resistance training include improvement in muscle strength and endurance, improvements in functional status and maintenance/improvement in bone density**
- **Multi-joint exercises are recommended over exercises focused on a single joint**
- **All major muscle groups (chest, shoulders, arms, back, abdomen, and legs) should be incorporated into a resistance training program**
- **Larger muscle groups (legs, back, and chest) should be worked before smaller muscle groups (arms and shoulders)**
- **Resistance training prescription**
  - **Frequency: 2–3 times/week**
  - **Intensity: 2–3 sets of 10–15 repetitions per set**
  - **Time: 20 minutes per session**
  - **Rest: 2- to 3-minute rest period between sets and exercises**
- **For survivors who do not currently do resistance training: Start with one set of each exercise and progress up to 2–3 sets as tolerated**
- **Utilize weight amount that would allow for performance of 10–15 repetitions**
- **Survivors at risk for or with lymphedema should utilize compression garments when engaging in resistance training**

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GENERAL PRINCIPLES OF NUTRITION

- **Assess daily intake of fruits, vegetables, food/beverages with added fats/sugars, processed foods, red meat, alcohol use, and desserts**
- **Assess eating habits, including portion size, night grazing, snacking habits, frequency of eating out**
- **Encourage informed choices about food to ensure variety and adequate nutrient intake**
- **Recommended composition of diet[a,b,c]**
  - **2/3 (or more) vegetables, fruits, whole grains, or beans**
  - **1/3 (or less) animal protein**
- **Recommended sources of dietary components:**
  - **Fat: plant sources such as olive or canola oil, avocados, seeds and nuts, and fatty fish[d]**
  - **Carbohydrates: fruits, vegetables, whole grains, and legumes**
  - **Protein: poultry, fish, legumes, low fat dairy foods, and nuts**
- **Limit intake of red or processed meat**
- **Currently there is no consensus either refuting or supporting the role of soy foods in cancer control. Thus, moderate consumption (3 or less servings per day) of soy foods is considered prudent.**

[a] Recommendation for healthy food portion sizes can be found on the American Institute of Cancer Research (AICR) website (http://www.aicr.org/new-american-plate/reduce_diet_new_american_plate_portion.html) as well as the USDA "Choose My Plate" website www.choosemyplate.gov.

[b] Encourage the use of healthy recipes from resources such as the American Cancer Society's "Find Healthy Recipes" website: http://www.cancer.org/healthy/eathealthygetactive/eathealthy/findhealthyrecipes/maindishes/index

[c] For patients desiring more precise recommendations for dietary composition guidelines:

- Fat: 20%–35% of total energy intake with saturated fat <10% and trans fat <3%;
- Carbohydrates : 45%–65% of total intake with high intake of fruits, vegetables, and whole grains;
- Protein: 10%–35% of total intake and goal of 0.8 g/kg

(Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242-274. Available at: http://onlinelibrary.wiley.com/doi/10.3322/caac.21142/full).

[d] These foods are high in calories and should be limited if weight control is an issue.

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GENERAL PRINCIPLES OF WEIGHT MANAGEMENT

- **Weight gain after cancer diagnosis and treatment is common; providers should discuss strategies to prevent weight gain for normal weight and overweight/obese survivors.**
- **Weight gain can exacerbate risk for functional decline, comorbidity, and possibly cancer recurrence or death; and can reduce quality of life.**
- **Weight management should be a priority for all cancer survivors**
  - **Weight gain should be a priority for underweight survivors.**
  - **Maintenance of weight should be encouraged for normal weight survivors.**
  - **Weight loss should be a priority for overweight/obese survivors.**
- **Principles of weight loss:**
  - **Limit foods that are high in calories, particularly those that provide relatively few nutrients such as sugar sweetened beverages and food with added fats and sugars (ie, many desserts, fried foods, fast foods).**
  - **Substitute high-calorie foods with low-energy dense foods such as water-rich vegetables, fruits, soups, and whole grains.**
  - **Practice portion control by using smaller plates and restricting intakes to one serving.**
  - **Make informed food choices through routine evaluation of food labels.**
- **Referrals to registered dietitians, especially those who are Certified Specialists in Oncology Nutrition (CSO) and members of the Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics, should be considered.[d]**
- **There is no current evidence to support the use of weight loss supplements in cancer survivors.**

[d]Many hospitals employ CSOs and those in private practice can be accessed via the Academy of Nutrition and Dietetics locator at www.eatright.org.

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NUTRITION AND WEIGHT MANAGEMENT ASSESSMENT[e]

INTERVENTIONS

Evaluate weight status based on body mass index (BMI) criteria[f]

Clinical Evaluation:

- Assess current dietary and physical activity habits and ask about:
  - Daily food intake and eating habits
  - Physical activity habits
  - Willingness to address weight (if necessary) and past strategies used to change[g]
  - Barriers to nutrition and weight management:
    - Access to nutrient dense foods
    - Financial and socioeconomic issues
    - Time
  - Appetite and changes in eating patterns

Assess treatment effects and medical issues:

- Effects of treatment
  - GI dysmotility
  - Swallowing issues/dysphagia
  - Oropharyngeal anatomic changes
  - Bowel dysfunction
  - Digestive enzyme insufficiency
  - GI tract reconstruction/anastomoses
- Comorbidities:
  - Cardiovascular disease
  - Diabetes
  - Renal disease
  - Liver disease
  - Mood disorders (eg, anxiety and depression)
  - Thyroid dysfunction
  - GI disease
- Medication use
- Dental health
- Supplement use

Overweight/Obese → See SNWM-4

Normal weight → See SNWM-4

Underweight → See SNWM-4

[e]Coordination with primary care physicians and other involved providers is recommended.
[f]For body mass index, see (SNWM-A).
[g]For additional resources see the ASCO Toolkit on Obesity and Cancer: http://www.asco.org/practice-research/obesity-and-cancer and the LIVESTRONG My Plate Calorie Tracker: http://www.livestrong.com/myplate.

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NUTRITION AND WEIGHT MANAGEMENT INTERVENTIONS[g,h]

Overweight/ Obese →

- Discuss "General Principles of Nutrition" (See SNWM-1)
- Discuss "General Principles of Weight Management" (See SNWM-2)
- Discuss "General Principles of Physical Activity" (See SPA-1)
- Discuss portion control[i]
- Refer to community resources
- Refer to dietitian or weight management programs for individualized help as needed[j]
- Consider evaluation for bariatric surgery or pharmacologic therapy[k] as appropriate (if obese or morbidly obese)[i]

Normal weight →

- Discuss "General Principles of Nutrition" (See SNWM-1)
- Discuss "General Principles of Physical Activity" (See SPA-1)
- Reinforce maintenance of normal body weight throughout lifetime

Underweight →

- Discuss "General Principles of Nutrition" (See SNWM-1)
- Discuss increasing frequency of feeding[i]
- Discus avoiding fluid intake with meals
- Assess smoking status and offer smoking cessation assistance as appropriate
- Assess dental health and risk factors for poor oral intake
- Assess swallowing, taste/smell disorders, and GI motility as appropriate
- Consider referral to dietitian for individualized counseling

[g] For additional resources see the ASCO Toolkit on Obesity and Cancer: http://www.asco.org/practice-research/obesity-and-cancer and the LIVESTRONG My Plate Calorie Tracker: http://www.livestrong.com/myplate.
[h] Coordination with primary care physicians and other involved providers is recommended.
[i] Modification of diet and dietary components should be done on an individual basis.
[j] Strongly consider for survivors with negligible weight loss from diet and exercise interventions.
[k] The safety and efficacy of these drugs in cancer survivors is unknown. Lifestyle modifications is preferred over pharmacologic therapy.

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GENERAL PRINCIPLES OF SUPPLEMENT USE

- **Supplement use is not recommended for most survivors, except in instances of documented deficiencies, inadequate diet, or comorbid indications (eg, osteoporosis, ophthamologic disorders, cirrhosis).**
- **Little data exist to support the use of vitamins or other dietary supplements for the purposes of cancer control, recurrence, or prevention.**
- **Taking vitamin supplements does not replace the need for adhering to a healthy diet. All efforts should be made to obtain nutrients from dietary intake[a]**
- **Providers should assess supplement use at regular intervals. Ask about reasons for supplement use and supplement ingredients.[b]**
- **Survivors of certain cancers are at risk for vitaman deficiencies based on their cancer treatment. Deficiencies should be assessed and repleted as needed (For example, See GAST-6 from the NCCN Guidelines for Gastric Cancer).**

[a]Referral to registered dietitians, especially those who are Certified Specialists in Oncology Nutrition (CSO) should be considered for guidance in supplement use, if deemed necessary.
[b]Consider use of available resources for information on supplements (See SURV-B 2 of 2).

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BODY MASS INDEX (BMI)[1,2]

To find an individual's BMI on this chart, find the height on the left hand column and follow across to the column representing the appropriate weight. The category into which the survivor fits – underweight, normal weight, overweight, or obese – can be seen at the bottom of the chart.

Height	Weight in Pounds																																				
	85	90	95	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215	220	225	230	235	240	245	250	255	260	265
4' 10"	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55
4' 11"	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	53	54
5'	17	18	19	20	21	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
5' 1"	16	17	18	19	20	21	22	23	24	25	26	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	43	44	45	46	47	48	49	50
5' 2"	16	16	17	18	19	20	21	22	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	37	38	39	40	41	42	43	44	45	46	47	48	48
5' 3"	15	16	17	18	19	19	20	21	22	23	24	25	26	27	27	28	29	30	31	32	33	34	35	35	36	37	38	39	40	41	42	43	43	44	45	46	47
5' 4"	15	15	16	17	18	19	20	21	21	22	23	24	25	26	27	27	28	29	30	31	32	33	33	34	35	36	37	38	39	39	40	41	42	43	44	45	45
5' 5"	14	15	16	17	17	18	19	20	21	22	22	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	37	37	38	39	40	41	42	42	43	44
5' 6"	14	15	15	16	17	18	19	19	20	21	22	23	23	24	25	26	27	27	28	29	30	31	31	32	33	34	35	36	36	37	38	39	40	40	41	42	43
5' 7"	13	14	15	16	16	17	18	19	20	20	21	22	23	23	24	25	26	27	27	28	29	30	31	31	32	33	34	34	35	36	37	38	38	39	40	41	42
5' 8"	13	14	14	15	16	17	17	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33	34	35	36	36	37	38	39	40	40
5' 9"	13	13	14	15	16	16	17	18	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	32	33	34	35	35	36	37	38	38	39
5' 10"	12	13	14	14	15	16	16	17	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32	33	34	34	35	36	37	37	38
5' 11"	12	13	13	14	15	15	16	17	17	18	19	20	20	21	22	22	23	24	24	25	26	26	27	28	29	29	30	31	31	32	33	33	34	35	36	36	37
6'	12	12	13	14	14	15	16	16	17	18	18	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30	31	31	32	33	33	34	35	35	36
6' 1"	11	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30	30	31	32	32	33	34	34	35
6' 2"	11	12	12	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	22	23	24	24	25	26	26	27	28	28	29	30	30	31	31	32	33	33	34
6' 3"	11	11	12	12	13	14	14	15	16	16	17	17	18	19	19	20	21	21	22	22	23	24	24	25	26	26	27	27	28	29	29	30	31	31	32	32	33
	Underweight													Normal weight										Overweight								Obese						

[1]BMI was calculated using the following formula: weight in pounds (lbs) X 703 / height in inches squared. The weight categories are as follows:

- Underweight (BMI <18.5 kg/m^2)
- Normal weight (BMI 18.5–24.9 kg/m^2)
- Overweight (BMI 25–29.9 kg/m^2)
- Obese (BMI ≥30 kg/m^2)

[2]For weight ranges that fall outside of the table above, the following BMI calculator from the Centers for Disease Control and Prevention may be used: http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html.

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GENERAL PRINCIPLES OF IMMUNIZATIONS

- **These principles apply to cancer survivors, including those with hematologic or solid tumor malignancies and those post transplant.**
- **Clinicians should consider and encourage the administration of inactivated vaccines (eg, influenza), vaccines made of purified antigens (eg, pneumococcus), bacterial components (eg, diphtheria-tetanus-pertussis), or genetically engineered recombinant antigens (eg, hepatitis B) in all cancer and transplant survivors. In the absence of known harm, administration of inactivated vaccines with the hope of achieving some protection may be worthwhile. The usual doses and schedules are recommended.[a,b,c]**
- **Vaccines as a strategy to prevent infection represents a unique challenge in cancer and transplant survivors. Vaccines may not trigger protective immune responses in actively immunocompromised individuals or in survivors with residual immune deficits. In addition, certain vaccines such as those that are live attenuated (eg, zoster, MMR) are contraindicated in actively immunosuppressed individuals because of a proven or theoretical increased risk of prolonged shedding and disease from the live organism present in the vaccine; other live attenuated vaccines might also be contraindicated in survivors' close contacts (eg, oral polio vaccine).**
- **Ideally, clinicians should have administered all indicated vaccines to patients before initiation of cancer treatment (if possible, at least two weeks before cancer treatment).[d]**
  - **Inactivated or recombinant vaccines should be administered 2 or more weeks before cancer treatment and 3 or more months after cancer chemotherapy. While this schedule is preferred, the inactivated influenza vaccine can be administered during cancer treatment.**
  - **Live viral vaccines can be administered 4 or more weeks before cancer treatment or 3 or more months after cancer chemotherapy, but consultation with an infectious disease specialist or physician familiar with vaccination in survivors and/or patients with cancer is recommended.**
- **In survivors who received anti-B cell antibody therapy, vaccination should be delayed for at least 6 months after chemotherapy and the last dose of such therapy.**

[a] General Recommendations on Immunization--Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21293327.

[b] Recommended Adult Immunization Schedule for Adults 19 years or Older: United State, 2014: http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf and Bridges CB, Coyne-Beasley T; Advisory Committee on Immunization Practices. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older: United States, 2014. Ann Intern Med. 2014;160:190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24658695

[c] Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:309-18.

[d] Cancer treatment includes chemotherapy, surgery, treatment with immunosuppressive drugs, radiation, and splenectomy.

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RISK ASSESSMENT AND SCREENING

Risk factors for infections:
- **Underlying disease**
- **Prior chemotherapy**
- **Monoclonal antibodies (eg, rituximab, alemtuzumab)**
- **Prior radiation**
- **Corticosteroids**
- **Prior hematopoietic cell transplantation (HCT)[e]**
- **Prior/current exposure to endemic infections or epidemics**
- **Blood transfusion history**

→

INTERVENTIONS

- **Education on infection prevention practices**
  - ➤ **Safe pet care/avoidance of zoonosis[f]**
  - ➤ **Travel precautions[g]**
  - ➤ **Gardening precautions[h]**
- **Vaccines[i,j]**
  - ➤ **Assess overall immune system viability and history of allergic reactions to vaccines**
    - ◊ **Baseline WBC should be adequate before starting vaccinations, unless elevated due to disease status**
    - ◊ **Patient should not be on immunosuppressive drugs[k] or chemotherapy**
    - ◊ **Ongoing infection should not be present**
- **Antimicrobial prophylaxis**
  (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections)

→ **See SIMIN-3**

[e] HCT includes peripheral blood stem cell transplantation, bone marrow transplantation (BMT), and cord blood transplantation.

[f] Safe pet care tips include washing hands with soap and running water after handling animals and their feces. If possible, survivors should avoid direct contact with animal feces.

[g] Travel precautions include education on the need for pre-travel vaccines, prophylaxis against specific infections, and education on how to prevent waterborne, airborne, and zoonotic infections. Travelers may find useful information at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-8-advising-travelers-with-specific-needs/immunocompromised-travelers or by consulting a travel clinic.

[h] Examples of gardening precautions include:
- Wearing gloves to avoid skin cuts/punctures that could have delayed healing and to avoid thorns than can have fungus or staphylococcus/streptococcus.
- Wearing a protective mask to avoid spores. (For guidelines on physical activity see [SPA-1])

[i] See General Principles of Vaccines in Cancer Survivors (SIMIN-A).

[j] See Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors/Vaccines That Can Be Used With Caution In Close Contacts of Immunocompromised Survivors (SIMIN-B).

[k] Immunosuppressive drugs include ≥0.5 mg/kg of prednisone or equivalent, or greater than a combination of two immunosuppressive medications given concurrently.

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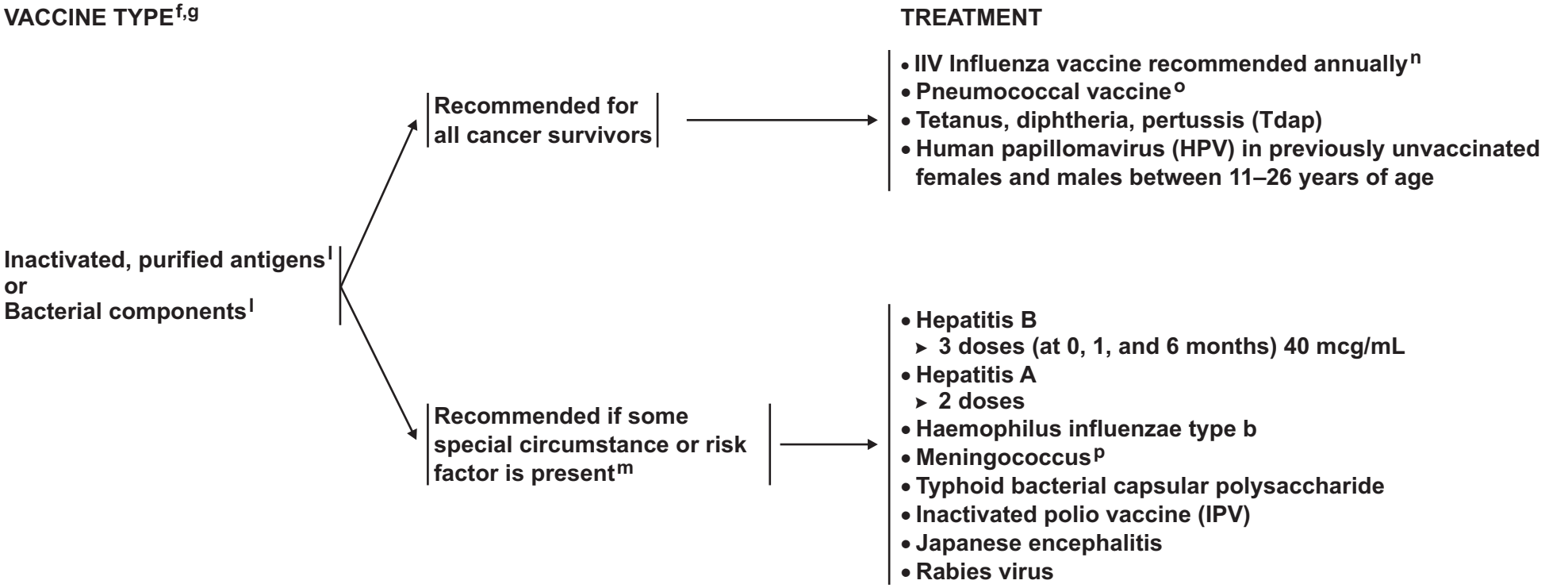

[i] See General Principles of Vaccines in Cancer Survivors (SIMIN-A).
[j] See Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors/Vaccines That Can Be Used With Caution In Close Contacts of Immunocompromised Survivors (SIMIN-B).
[l] Inactivated or purified antigens or bacterial components should be administered beginning at least 3 months after chemotherapy or radiation therapy and 6 months after hematopoietic cell transplantation (HCT) (a dose of inactivated influenza vaccine can be given as early as 4 months after HCT, but a second dose should be considered in this situation).
[m] These vaccines should be considered if there are unique circumstances in patient's lifestyle, upcoming travel, or local epidemic or risks that merit their use. Please consult with an infectious disease or travel medicine specialist.
[n] See Principles of Influenza Vaccine(s) (SIMIN-C).
[o] PCV-13 and PPSV-23 are recommended for adults with immunocompromising conditions (ie, HCT and functional or anatomic asplenia.) Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012;61:816-819. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23051612.
[p] Recommended in high-risk patients.

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GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccination in Non-Transplant Survivors[1,2]

- **These principles apply to survivors of hematologic or solid tumor malignancies except those receiving anti-B-cell antibodies.[3]**

- **The following vaccines can be administered to cancer survivors:**
  - **Influenza vaccine annually (See Principles of Influenza Vaccine(s) SIMIN-C)**
  - **Pneumococcal vaccine**
    - **13-valent pneumococcal conjugate vaccine (PCV13) x 1dose if never vaccinated against pneumococcus**
    - **PPSV23 should be administered at least 8 weeks after the indicated dose(s) of PCV13**
    - **For those who received pneumococcal polysaccharide vaccine-23 (PPSV23), PCV13 should be administered ≥1 year after the last PPSV23 dose**
  - **Tetanus, diphtheria, pertussis vaccine (Td/Tdap):**
    - **Administer a one-time dose of Tdap to adults younger than age 65 years who have not received Tdap previously or for whom vaccine status is unknown to replace one of the 10-year Td boosters (substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years). Otherwise Td booster every 10 years.**
  - **Consider human papillomavirus (HPV) vaccine in survivors 11–26 years of age**
    - **Female 3 doses**
    - **Male 3 doses**

[1] Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012;61:816-819. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23051612.

[2] Bridges CB, Coyne-Beasley T; Advisory Committee on Immunization Practices. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older: United States, 2014. Ann Intern Med 2014;160:190. http://www.ncbi.nlm.nih.gov/pubmed/24658695.

[3] In survivors who received anti-B cell antibody therapy, the above vaccines can be given, but should be delayed for at least 6 months after chemotherapy and the last dose of such therapy.

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

GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccination in Hematopoietic Cell Transplant (HCT) Survivors[4,5]

- **Influenza vaccine annually**
  (See Principles of Influenza Vaccine(s) SIMIN-C)
  - **One dose should be administered annually to all cancer survivors starting 6 months after HCT and starting 4 months after if there is a community outbreak of influenza as defined by the local health department.**
- **Pneumococcal vaccine**
  - **Three doses (1 month apart) of PCV13 should be administered 3–6 months after HCT.**
  - **At 12 months after HCT, 1 dose of PPSV23 should be given provided the patient does not have chronic graft-versus-host disease (GVHD).**
  - **For patients with chronic GVHD, a fourth dose of PCV13 can be given at 12 months after HCT.**
- **Haemophilus influenzae type b (Hib) vaccine**
  - **Three doses of Hib vaccine should be administered 6–12 months after HCT**
- **Meningococcal conjugate vaccine quadrivalent (MCV4)**
  - **The MCV4 vaccine may be considered in outbreak situations or in endemic areas.**
- **Tetanus, diphtheria, pertussis (Td/Tdap) vaccine**
  - **Three doses of tetanus/diphtheria–containing vaccine should be administered 6 months after HCT (administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second). This three-dose-regimen should be followed by Td boosters every 10 years.**
  - **Administration of 3 doses of DTaP should be considered (can replace second and third dose by Td).**
- **Hepatitis B vaccine**
  - **Three doses of HepB vaccine should be administered 6–12 months after HCT.**
  - **If a postvaccination anti-Hepatitis B surface antigen (anti-HBs) concentration of ≥10 mIU/mL is not obtained, a second 3-dose series of HepB vaccine is recommended:**
  - **1st dose of HepB vaccine (after which anti-HBs is tested) using high dose (40 µg) should be administered.**
- **Inactivated Polio Vaccine (IPV)**
  - **Three doses of IPV vaccine should be administered 6–12 months after HCT**
- **Consider human papillomavirus (HPV) vaccine**
  - **Consider administration of 3 doses of HPV vaccine 6–12 months after HCT for female patients aged 11–26 years and HPV vaccine for males aged 11–26 years**
- **Live viral vaccines should not be administered to HCT survivors with active GVHD or ongoing immunosuppression. They should only be administered to HCT survivors without active GVHD or ongoing immunosuppression following consultation with an infectious diseases specialist.**
  - **Measles, mumps, rubella (MMR) vaccine**
    - **A 2-dose series of MMR vaccine should be administered to measles-seronegative adolescents and adults 24 months after HCT in patients with neither chronic GVHD nor ongoing immunosuppression and 8–11 months after the last dose of immune globulin intravenous (IGIV).**
  - **Zoster vaccine (VAR)**
    - **A 2-dose series of VAR should be administered 24 months after HCT to varicella-seronegative patients with neither GVHD nor ongoing immunosuppression and 8–11 months after the last dose of IGIV.**

[4]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:309-18. http://www.ncbi.nlm.nih.gov/pubmed/24421306.

[5]HCT includes peripheral blood stem cell transplantation, bone marrow transplantation (BMT), and cord blood transplantation.

Note: All recommendations are category 2A unless otherwise indicated.
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GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccines Considered Safe For Cancer And Transplant Survivors And Close Contacts[6]

Inactivated or purified antigens or bacterial components[7]

- **Influenza: inactivated influenza virus vaccine**
  - **Trivalent (IIV3), Standard Dose**
  - **Trivalent (IIV3), High Dose**
  - **Quadrivalent (IIV4), Standard Dose**
- **Pneumococcus:**
  - **Pneumococcal conjugate vaccine (PCV)**
  - **PPSV**
- **Meningococcus:**
  - **Quadrivalent meningococcal conjugate vaccine (MCV4)**
  - **Quadrivalent meningococcal polysaccharide vaccine (MPSV4)**
- **Tetanus, diphtheria, pertussis (Td/Tdap)**
- **Hepatitis A**
- **Haemophilus influenzae type b**

Recombinant viral antigens

- **Hepatitis B**
- **Human papillomavirus (HPV) female and HPV male**
- **Recombinant trivalent Influenza Vaccine (RIV3)[8]**

[6] Ideally, clinicians should have administered all indicated vaccines to patients at least 2 weeks before initiation of cancer treatment (ie, chemotherapy, surgery, treatment with immunosuppressive drugs, radiation, splenectomy).

[7] For patients traveling to endemic countries, vaccines such as typhoid bacterial capsular polysaccharide, inactivated polio vaccine (IPV), Japanese encephalitis, and rabies virus are recommended by the Centers for Disease Control and Prevention (www.cdc.gov).

[8] This vaccine is recommended for patients with egg allergies.

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

VACCINES CONTRAINDICATED OR TO BE USED WITH CAUTION IN ACTIVELY IMMUNOCOMPROMISED SURVIVORS

Live attenuated vaccines[1]

- **Influenza: live, attenuated influenza vaccine (LAIV)**
- **Measles, Mumps, Rubella**
- **Zoster**[2]
- **Oral polio**
- **Rotavirus**
- **Oral typhoid**
- **Yellow fever**

VACCINES THAT CAN BE USED WITH CAUTION IN CLOSE CONTACTS OF IMMUNOCOMPROMISED SURVIVORS[3]

- **Live, attenuated influenza vaccine (LAIV)**
- **Combined measles, mumps, and rubella (MMR) vaccines**
- **Varicella vaccine (VAR)**[4]
- **Zoster vaccine (ZOS)**[4]
- **Yellow fever vaccine and oral typhoid vaccine for travel**

[1] Severe complications have followed vaccination with live attenuated vaccines among immunocompromised patients. They should not be offered to an actively immunocompromised or transplant survivor or their close contacts, unless cleared by a clinician experienced in vaccine use or by an infectious disease specialist. If a live attenuated vaccine is inadvertently administered to a survivor's close contact, close contact with the survivor should be avoided for 2 to 6 weeks following vaccination depending on the type of administered vaccine.

[2] For additional recommendations regarding Zoster vaccine, See Principles of Zoster (Shingles) Vaccine Use in Cancer or Transplant Survivors (SIMIN-D).

[3] Rubin et al, 2013 IDSA Clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.

[4] Immunocompromised patients should avoid contact with persons who develop skin lesions after receipt of Varicella or Zoster vaccine, until the lesions clear.

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

PRINCIPLES OF INFLUENZA VACCINE(S)[1,2]

- **Annual influenza vaccination is recommended[3] for all cancer and transplant survivors. Live attenuated influenza vaccines should be avoided in these individuals unless they have been cleared to do so by an infectious disease specialist or physician familiar with vaccination in this population.**
- **For a summary of recommendations for prevention and control of influenza with vaccines see: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm**
- **Components of the influenza vaccine are determined each year by the World Health Organization (WHO) according to reports of the most common influenza viruses that are likely to circulate that year.**
- **Influenza vaccines can be inactivated, recombinant or live-attenuated. They may contain standard or higher doses of the antigen. They can be trivalent or quadrivalent.**

Preferred Vaccines

- **Inactivated influenza vaccine**
  - **Trivalent (IIV3), Standard Dose**
  - **Trivalent (IIV3), High Dose**
  - **Quadrivalent (IIV4), Standard Dose**
- **Recombinant influenza vaccine[4]**
  - **Trivalent (RIV3)**

To date, we do not have evidence that one vaccine is superior to any other vaccine. Health care providers should primarily choose one of the inactivated or recombinant vaccines and avoid giving the live-attenuated virus vaccine to cancer and transplant survivors.

[1] IIV influenza vaccine recommended except for patients with severe egg allergies.

[2] Bridges CB, Coyne-Beasley T; Advisory Committee on Immunization Practices. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older: United States, 2014. Ann Intern Med. 2014;160:190. http://www.ncbi.nlm.nih.gov/pubmed/24658695.

[3] Barr IG; Writing Committee of the World Health Organization Consultation on Northern Hemisphere Influenza Vaccine Composition for 20132014. WHO recommendations for the viruses used in the 2013-2014 Northern Hemisphere influenza vaccine: Epidemiology, antigenic and genetic characteristics of influenza A(H1N1)pdm09, A(H3N2) and B influenza viruses collected from October 2012 to January 2013. Vaccine. 2014 Feb 28. pii: S0264-410X(14)00187-X. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/24582632.

[4] This vaccine is recommended for patients with egg allergies.

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

PRINCIPLES OF ZOSTER (SHINGLES) VACCINE USE IN CANCER OR TRANSPLANT SURVIVORS[1,2]

- **Zoster vaccine may be considered in survivors with a history of solid tumors or leukemia whose disease is in remission, who have restored their immunocompetence, and who have not received chemotherapy or radiation for at least 3 months.**
- **If zoster vaccine is given prior to starting therapy, it should be administered at least 4 weeks prior to the first dose of immunosuppressive therapy.[2]**
- **The vaccine can be administered to select immunocompetent survivors regardless of whether they report a prior episode of herpes zoster.[3]**
- **Licensed antiviral medications active against members of the herpes virus family (eg, acyclovir, famciclovir, valacyclovir, valganciclovir) might interfere with replication of the live, varicella zoster virus (VZV)-based zoster vaccine.[4]**

- **A single dose of zoster vaccine is recommended for cancer or transplant survivors 60 years of age and older assuming that active or ongoing immunodeficiency is not present and that there is no history of cellular immunodeficiency.**
  - **For survivors age 50–59 years, zoster vaccination should be considered in those with a history of varicella or zoster infection or VZV seropositive with no previous doses of varicella vaccine.**

- **Zoster vaccine should be avoided**
  - **in patients with lymphomas, other malignant neoplasms affecting the bone marrow or lymphatic system, or history of cellular immunodeficiency**
  - **in patients on immunosuppressive therapy, including high-dose corticosteroids (>20 mg/day of prednisone or equivalent) lasting two or more weeks**
  - **in patients undergoing or with history of HCT. The experience of HCT recipients with VZV-containing vaccines (eg, zoster vaccine) is limited. Physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks. If a decision is made to vaccinate with zoster vaccine, the vaccine should be administered at least 24 months after transplantation in patients without active graft-versus-host disease (GVHD) or enhanced immunosuppression.**

[1] Hales CM, Harpaz R, Ortega-Sanchez I. Update on recommendations for use of herpes zoster vaccine. MMWR Morb Mortal Wkly 2014;22:63:729-731.
[2] Rubin et al, 2013 IDSA Clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.
[3] Zoster vaccination is not indicated to treat acute zoster, to prevent persons with acute zoster from developing postherpetic neuralgia (PHN, a common complication of zoster that results in chronic, often debilitating pain that can last months or even years), or to treat ongoing PHN. Before routine administration of zoster vaccine, it is not necessary to ask patients about their history of varicella (chickenpox) or to conduct serologic testing for varicella immunity. Hales CM, Harpaz R, Ortega-Sanchez I. Update on recommendations for use of herpes zoster vaccine. MMWR Morb Mortal Wkly 2014;22:63:729-731.
[4] Survivors taking chronic acyclovir, famciclovir, valacyclovir, or valganciclovir should discontinue these medications at least 24 hours before administration of zoster vaccine. These medications should not be used for at least 2 weeks after vaccination, by which time the immunologic effect should be established.

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

A report issued by the U.S. Centers for Disease Control and Prevention (CDC) and the National Cancer Institute (NCI) and data from the American Cancer Society estimate that the number of cancer survivors in the United States increased from approximately 3 million in 1971 to nearly 14.5 million in 2014.[1,2] These numbers are predicted to reach almost 19 million by 2024.[2] This striking increase is generally attributed to rising cancer incidence rates (mainly resulting from an aging population), earlier detection, and better treatment.

An analysis of the SEER database showed that approximately 46% of survivors were 70 years of age or older in 2012.[2] In fact, an estimated 1 of every 5 persons older than 65 years is a cancer survivor. Only 5% are younger than 40 years, and survivors of childhood cancer constitute between 0.5% and 3.0% of the survivor population.[2,3] The most common cancer sites in the survivor population are breast, prostate, colon/rectum, and melanoma, together accounting for approximately 58% of survivors.[2] Approximately 64% of survivors were diagnosed 5 or more years ago, whereas 15% of survivors were diagnosed 20 or more years ago, and approximately 5% have survived 30 years or longer.[2]

Unfortunately, many of these cancer survivors experience physical and/or psychosocial late and/or long-term effects of cancer and its treatment, which can be severe, debilitating, and sometimes permanent. Survivors may be discharged from the care of their oncologist and feel isolated and scared. Furthermore, their primary care physicians (PCPs), who may now be responsible for their care, often do not know how best to care for the specific concerns and needs of cancer survivors.[4] ASCO's recent statement, "Achieving High-Quality Cancer Survivorship Care," cites a need for standardized, evidence-based practice guidelines for the management of treatment effects and health promotion of survivors.[5] ASCO, NCCN, and other groups that are working in parallel hope to provide this guidance.

The NCCN Survivorship Panel is comprised of a multidisciplinary panel of experts that includes at least one oncologist, bone marrow transplant clinician, gynecologist, urologist, infectious disease specialist, cardiologist, PCP, psychologist, exercise physiologist, nutrition scientist, nurse, epidemiologist, and patient advocate. The panel defined general principles of cancer survivorship to help guide the recommendations that form the basis for these guidelines.[6]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Survivorship, an electronic search of the PubMed database was performed to obtain key literature in the field of cancer survivorship published between September 1, 2013 and September 1, 2104, using the following search terms: ((("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND ("survivors"[MeSH Terms] OR "survivors"[All Fields] OR "survivor"[All Fields])) OR ((("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND ("survivorship"[All Fields])). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[7]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 165 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

General Principles of These Guidelines

These NCCN Guidelines for Survivorship provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in specialty cancer survivor clinics and primary care practices. The recommendations in these guidelines therefore pertain to patients who may be in remission and those who are cured. The guideline recommendations may also be applicable to those survivors for whom cancer has become a chronic condition and are living with metastatic disease. These guidelines are designed to provide a framework for the management of long-term and/or late effects of cancer and its treatment. The guidelines focus on the vast and persistent impact both the diagnosis and treatment of cancer can have on the adult survivor's health, physical and mental states, health behaviors, professional and personal identity, sexuality, and financial standing.

These guidelines should be used as a supplement to the follow-up recommendations within the disease-specific guidelines (see NCCN Guidelines for Treatment of Cancer by Site, available at www.NCCN.org) and should provide a framework for the coordination of care between the survivor's health care providers to ensure that needs are appropriately addressed. Although these guidelines are focused on survivors who are in clinical remission after the completion of cancer treatment, the topics, assessments, and interventions may also be applicable to survivors living with metastatic disease, as clinically appropriate (also see NCCN Guidelines for Supportive Care, available at www.NCCN.org).

These guidelines are not intended to provide guidance for the care of survivors of childhood cancer (detailed guidelines for the care of childhood cancer survivors are available from the Children's Oncology Group at http://www.survivorshipguidelines.org/). For survivorship issues related to younger populations, please also see the NCCN Guidelines for Adolescent and Young Adults (available at www.NCCN.org).

For this version of the NCCN Guidelines for Survivorship, the panel focused on several common issues of survivors: 1) anxiety and depression, 2) anthracycline-induced cardiac toxicity, 3) cognitive decline, 4) fatigue, 5) pain, 6) female and male sexual dysfunction, and 7) sleep disorders; and on the preventive health issues of immunizations and prevention of infections and healthy lifestyle behaviors. Additional topics will be addressed in subsequent updates.

Cancer Survivors

The NCCN Survivorship Panel supports the NCI's definition of a cancer survivor: "An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in this definition."[8] Throughout these guidelines, however, "survivor" refers to an individual with a

history of cancer; family, friends, and caregivers are not currently addressed.

The Effects of Cancer and Its Treatment

For some survivors, the consequences of cancer are minimal; these patients can return to a normal life after the completion of treatment. In fact, most cancer survivors report being in good general health and experience good to excellent quality of life.[9,10] Also, a recent survey of 659 survivors of breast, colorectal, and prostate cancers found that a majority do not suffer from psychologic morbidity or have a large number of unmet supportive care needs.[11] Other studies have similarly found that most survivors enjoy a high quality of life without a large number of cancer-related symptoms.[12,13]

However, many survivors do experience physical and/or psychosocial effects of cancer and its treatment.[14,15] Some sequelae become evident during anticancer treatment (long-term effects), whereas others may not manifest for months or years after active therapy (late effects). The problems can range from mild to severe, debilitating, or even life-threatening. Some problems are temporary or improve with time, whereas other problems are progressive or permanent. This topic has been well reviewed.[10,16]

A recent review suggests that at least 50% of survivors experience some late effects of cancer treatment.[16] The most common problems in cancer survivors are depression, pain, and fatigue.[17] The exact prevalence of various effects of cancer and its treatment are hard to quantify, because few studies have addressed these issues in a longitudinal fashion, comparing patients with and without a history of cancer to differentiate between the effects of cancer and the effects of aging.[10] In general, the prevalence of late effects in cancer survivors is believed to have increased over time, likely because anticancer interventions have become more complex and intense with combinations of surgery, radiation, chemotherapy, hormone therapy, and targeted biologics.[18]

Physical Effects

Physical problems in cancer survivors include pain, musculoskeletal issues, fatigue, lack of stamina, urinary/bowel problems, lymphedema, premature menopause, cognitive deficits, and sexual dysfunction.[10,19-21] The effects of cancer treatment on the heart and bone are also well known.[22-25] The type of physical problems depends mainly on the treatment. For example, radiation to the pelvis can be associated with bowel, urinary, and sexual dysfunction and increased risk for second primary malignancies.[26,27]

Second Primary Cancers

Importantly, the overall incidence of second primary cancers in survivors is higher than in the general population because of genetic susceptibilities (eg, cancer syndromes), shared causative factors (eg, smoking, obesity, environmental exposures), and/or the mutagenic effects of cancer treatment.[28-31] Treatment-related subsequent primary cancers vary with the type and intensity of anticancer treatment and are associated in particular with radiation and specific chemotherapeutic agents.[32-38] These secondary malignancies are especially well studied in long-term survivors of childhood cancers.[39-42] Studies by individual cancer type show that the incidence of subsequent unrelated cancers ranges from 2% in survivors of malignant lymphoma to 30% in survivors of small cell lung cancer.[16]

Screening for second primary cancers should be a shared responsibility between primary and oncology care physicians (see the NCCN Guidelines for Detection, Prevention, and Risk Reduction, available at

www.NCCN.org). In addition, lifestyle modifications that reduce the risk of second primary cancers (eg, smoking cessation, physical activity, weight loss) should be encouraged.[43]

Psychosocial Effects

Cancer has positive effects on a significant portion of individuals, including strengthened relationships, a sense of gratitude or empowerment, and an increased appreciation for life.[44-49] Many survivors, however, experience psychologic distress after active treatment, and some experience a combination of positive and negative psychologic effects. Distress can result from the fear of recurrence or death or secondary to physical, social, or practical problems.[44,47,50] In fact, as many as 19% of survivors meet the criteria for post-traumatic stress disorder.[44,47,51-53] Practical and social problems of survivors include issues surrounding employment, finances, and health and life insurance.[44,54-57]

Fear of Recurrence

As many as 70% of post-treatment cancer survivors report high levels of fear of cancer recurrence, which can cause significant and enduring distress.[47,58-61] In addition, caregivers report distress from fear of cancer recurrence in their loved one.[62] These fears and their associated distress may cause patients and their caregivers to either avoid appropriate surveillance or to demand more intense surveillance than evidence supports.[61] In addition, survivors with high levels of fear of recurrence are more likely to be depressed and have a lower quality of life.[63]

Employment Issues and Return to Work

Cancer and its treatment often have an adverse effect on work status, performance, and satisfaction.[64] Survivors often take long breaks from or even leave their jobs during treatment, and returning to work after cancer treatment can be critical to restoring normalcy to the lives of survivors. However, survivors may be left with disabilities or late/long-term effects that decrease their employment prospects or ability to perform at their previous levels. Several studies have shown that unemployment rates for survivors are higher than for the general population.[64-66] Furthermore, those survivors who do return to work often encounter difficulties, such as physical or cognitive limitations, fatigue, depression, anxiety, and perceived or real discrimination.[64,67,68]

Several studies have addressed factors that predict a delayed return to work.[69-72] For example, a French population-based study revealed that clinical factors, such as severity of the cancer, receipt of chemotherapy, or the experience of adverse effects, were associated with a delay in return to work.[71] In addition, a systematic review of cohort studies found that survivors who were older, had a lower education level, or had a lower income were less likely to return to work.[72]

Financial Burden

A recent study in Washington state found that patients with cancer have a 2.6-fold increased risk of bankruptcy.[73] In another study, 38% of patients with stage III colon cancer reported financial hardship resulting from cancer treatment, defined as accruing debt, selling or refinancing a home, borrowing money from friends or family, or experiencing a ≥20% decline in annual income.[74] Another recent study found that, in addition to the average >$16,000 excess economic burden that patients feel in the early phases of cancer treatment, survivors (>1 year from diagnosis) have an average annual excess economic burden that exceeds $4,000.[75] Much of this excess burden was because of excess medical expenditures. In addition, analysis of data from the 2008-2011 Medical Expenditure Panel Survey (MEPS) found that average annual medical costs and productivity losses resulting from health problems were

significantly higher in survivors than in those without a history of cancer.[76]

Clearly, with lost wages and increased expenses, the financial burden on many cancer survivors is great. Recent data suggest that patients belonging to racial and ethnic minorities are more likely to suffer financial hardship after cancer treatment.[77]

Standards for Survivorship Care

In 2005, the Institute of Medicine (IOM) and the National Research Council compiled a report entitled, "From Cancer Patient to Cancer Survivor: Lost in Transition."[18] According to this report, the essential components of survivorship care are:

1. Prevention of new and recurrent cancers and other late effects
2. Surveillance for cancer spread, recurrence, or second cancers
3. Assessment of late psychosocial and physical effects
4. Intervention for consequences of cancer and treatment (eg, medical problems, symptoms, psychologic distress, financial and social concerns)
5. Coordination of care between primary care providers and specialists to ensure that all of the survivor's health needs are met.

In addition, the IOM report discusses the importance of policies that ensure access to and health insurance coverage for all aspects of survivorship care, including psychosocial services. Cancer survivors with untreated distress have poorer compliance with surveillance screenings and are less likely to exercise and quit smoking.[78] A 2008 IOM report, "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs,"[79] concluded that psychosocial screening and care should be a part of the new standard for quality cancer care and should be integrated into routine care across the trajectory of cancer, which includes the period after active treatment. See the NCCN Guidelines for Distress Management (available online at www.NCCN.org) and *Anxiety and Depression* below for recommendations on screening for and treating distress.

In September 2011, the LIVESTRONG Foundation convened a meeting of experts and stakeholders in the survivorship field to define essential elements of survivorship care. After 2 days of consensus building, the group agreed on the following elements that all medical settings must provide for cancer survivors, either directly or through referral (http://www.livestrong.org/what-we-do/our-approach/reports-findings/essential-elements-brief/):

1. Survivorship care plan, psychosocial care plan, and treatment summary
2. Screening for new cancers and surveillance for recurrence
3. Care coordination strategy that addresses care coordination with PCPs and primary oncologists
4. Health promotion education
5. Symptom management and palliative care

In 2012, the Commission on Cancer (CoC) of the American College of Surgeons updated their accreditation standards for hospital cancer programs (http://www.facs.org/cancer/coc/programstandards2012.html). Their patient-centered focus now includes the development and dissemination of a survivorship care plan for all patients completing primary therapy. This requirement is to be phased in by 2015.

Implementation of these standards for survivorship care has been challenging, and reasons for the difficulties have been described.[80] To move toward the goal of all cancer survivors receiving all essential components of care, advances must be made in: 1) survivorship research; 2) education of health care providers; 3) education and

empowerment of survivors; and 4) policies that address reimbursement and resource allocation issues.

Models of Survivorship Care and the Role of Primary Care Providers

Various models have been proposed to facilitate the implementation of all the essential components of survivorship care for the growing population of post-treatment cancer survivors. These include survivorship clinics within academic or community cancer centers, community survivorship clinics run by primary care clinicians, and survivorship care in the primary care setting.[81-83] In each case, survivorship care is delivered by either physicians or by advanced practice clinicians such as nurse practitioners. Each model has advantages and disadvantages, and no one model is clearly the best for all situations.

With the population of cancer survivors growing at a rapid pace, the demand for follow-up care is expected to increase. An increasing proportion of this care will likely be performed by primary care teams. Because studies have shown that primary care providers often do not know how best to care for the specific concerns and needs of cancer survivors,[4,84-86] education for primary health care providers regarding appropriate survivorship care will be increasingly important.

A study in the Netherlands found that patients with cancer 2 to 5 years after diagnosis increased their number of consultations with primary care compared with age- and sex-matched controls without cancer by 15% for colorectal cancer ($P < .05$), 24% for breast cancer ($P < .001$), and 33% for prostate cancer ($P < .001$).[87] These survivors also had more chronic conditions than controls. Although an American study using the SEER-Medicare database showed a smaller increase in primary care use by breast cancer survivors (10% increase in year 4 after diagnosis; $P < .05$),[88] these results show that PCPs are providing a substantial amount of survivorship care. In fact, according to IOM analyses of the 2001 and 2002 National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, approximately one-third of the more than 36 million cancer-related visits to physicians' offices were made to primary care.[18] Furthermore, a nationally representative survey by NCI and the American Cancer Society found that >50% of PCPs provide survivors with cancer-related follow-up care, often with co-management by oncologists.[89]

However, in a recent survey of survivors regarding their preferences for follow-up care, most participants said that the PCP should only provide care if the responsibility was shared with the oncologist.[90] One of the reasons commonly cited for this preference was that survivors believe their PCPs lack the needed expertise to deal with their specific issues. In addition, survivors cited a desire for continuity of care. Additional surveys of survivors of breast cancer in the United States and of survivors of breast, colorectal, and prostate cancer the United Kingdom found similar preferences for oncologist-driven follow-up care over PCP follow-up care.[91,92] Importantly, however, 2 randomized trials comparing survivorship care administered by PCPs (provided guidelines outlining appropriate follow-up care) versus oncologists found no difference in disease-related outcomes, including survival.[93,94]

Survivorship Care Plans

Because primary care offices are in fact already caring for cancer survivors, it is critical for information to be shared between oncology and primary care teams. Good communication at the oncology/primary care interface may allow survivors to feel the continuity of care they desire. The CoC accreditation standards include the provision of a

survivorship care plan at the completion of treatment, as recommended in the IOM report.[18] According to the report, the plan should include:

- A personalized treatment summary
- Information on possible late and long-term effects
- Information on signs of recurrence
- Guidelines for follow-up care
- Identification of providers
- Recommendations for healthy living
- Identification of supportive care resources.

Some data suggest that treatment summaries lead to improvements in outcomes for survivors such as having fewer emotional concerns and more often reporting that their needs have been met.[95] However, a randomized controlled trial of 408 survivors of breast cancer that assessed the effects of survivorship care plans found no differences on patient-reported outcomes, including cancer-specific distress, between patients who received a discharge visit and a care plan and those who received only a discharge visit.[96] Although criticisms of this trial, including the relevance of its outcome measures, have been published,[97-99] definitive data supporting the benefits of survivorship care plans are clearly lacking.[100,101] Furthermore, providing a survivorship care plan is time-consuming and resource-intensive and could have unforeseen harms.[99,102] In fact, a recent survey that included a nationally representative sample of 1130 oncologists found that fewer than 5% of them provide a written survivorship care plan to survivors.[103] The survey also included 1020 PCPs, who were 9-times more likely (95% CI, 5.74–14.82) to have survivorship discussions with survivors if they received a written care plan.

ASCO released a clinical expert statement on cancer survivorship care planning in 2014.[104] The group of experts identified barriers to the successful implementation of survivorship care planning (including the time it takes to complete one, the lack of reimbursement for doing so, and the uncertainty as to whose responsibility it is to prepare the plan) and revised the ASCO survivorship care plan template to help address some of these barriers. In addition, a recent pilot study assessed the use of electronic health records to reduce the time and effort involved with creating care plans.[105] Although many plan elements required manual entry by the oncologist, the median time to complete the plans was only 3 minutes (range 2 to 12 minutes).

Because of the lack of definitive evidence that survivorship care plans improve outcomes, the NCCN Survivorship Panel does not currently require the use of survivorship care plans for compliance with these guidelines, although the provision of a survivorship care plan to all survivors at the completion of treatment is recommended if appropriate resources are available. Data from ongoing trials will help inform future recommendations.

Surveillance for Cancer Recurrence

Screening for cancer recurrence is an important aspect of survivorship care. In general, this surveillance is performed by the oncology team. When surveillance is overseen by the primary care team, the oncologist should provide evidence-based recommendations based on currently available guidelines. Specific recommendations vary between cancer site and stage and are not addressed in these guidelines. Please see individual NCCN Guidelines for Treatment of Cancer by Site (available online at www.NCCN.org).

Assessment for Effects of Cancer and Its Treatment

All survivors should be assessed at least annually for symptoms related to cancer and prior cancer treatment, with appropriate follow-up care as

clinically indicated. This assessment can be done by the oncologist or primary care clinician. Shared, coordinated care between the oncology provider and primary care provider is encouraged. The panel does not assume that all survivorship issues will be addressed at every visit.

Some tools that screen for long-term and late physical and psychosocial effects of cancer and its treatment in survivors have been validated.[106-111] In addition, the NCCN Survivorship Panel created a sample screening instrument that is guideline-specific and can be self-administered or administered by an interviewer. This assessment tool was developed specifically for use in combination with the NCCN Guidelines for Survivorship to help providers deliver necessary and comprehensive survivorship care. Although this instrument has not yet been piloted or validated, the answers can be used to guide providers to topics within the guidelines that require more in-depth assessment via validated tools and/or clinical evaluation.

In addition to screening by history and physical examination, care providers should assess the following to determine whether reversible or contributing causes for symptoms exist:

1. Current disease status
2. Functional/performance status
3. Current medications, including over the counter medications and supplements
4. Comorbidities, including weight and tobacco use
5. Prior cancer treatment history and modalities used.

This information can also inform about the patient's risk for specific late or long-term effects, including risks for second primary cancers and comorbidities. For example, patients who received pelvic irradiation or surgery are at risk for sexual dysfunction; patients with a history of brain metastasis or cranial irradiation have an elevated risk for cognitive dysfunction. In general, those who underwent more intensive therapy are at higher risk for multiple late and/or long-term effects. Survivors undergoing certain treatments, such as mantle radiation or certain systemic therapies, may be at increased risk for secondary malignancies. Those survivors who continue to smoke are at increased risk for smoking-related comorbidities and second primary cancers.

Reassessment

Survivors should be followed and reassessed at regular intervals, depending on the nature and severity of late and long-term effects being treated. At each time point, assessment of disease status and ongoing effects of cancer and its treatment should be addressed. In addition, survivors should be periodically rescreened for the development of new late and long-term effects of cancer and its treatment. The outcomes of any interventions for ongoing effects of cancer and its treatment should be evaluated regularly based on best practices and available resources. Outcome assessment may include survivor satisfaction with the effectiveness of the intervention in reducing symptom burden, adequate pain control, receipt of recommended immunizations and preventive care, and improved adherence to guideline recommendations for health behaviors.

Survivorship Research

The IOM survivorship report cites a paucity of longitudinal cohort studies linking specific cancer types or treatments with specific late effect, making it difficult to predict risk for individual patients.[18] Research is needed to increase understanding of the prevalence of, mechanisms of, and risks factors for late and long-term effects of cancer and its treatment. In addition, research is needed to better define interventions that relieve symptoms, restore function, and improve the quality of life of

survivors.[112] Finally, research can help better define optimal follow-up and surveillance schedules for cancer survivors after treatment.[113,114]

In June 2012, the American Cancer Society, the CDC, the LIVESTRONG Foundation, NCI held a joint meeting and created an action plan to facilitate the translation of survivorship research into survivorship care.[115] The plan is driven by collaboration between researchers, survivors, clinicians, and public health professionals; the use of technology, such as electronic health records; analysis of information from the viewpoints of multiple stakeholders; and the integration and synthesis of knowledge through the use of systematic reviews and meta-analyses.

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Recommendations for Specific Effects of Cancer and Its Treatment

Randomized controlled trials have provided evidence for the effectiveness of interventions for cancer survivors to lessen symptoms such as depression, fatigue, pain, sleep disorders, and sexual dysfunction.[114] The NCCN Survivorship Panel used such evidence as the basis for the recommendations in these guidelines. When evidence in survivorship populations was lacking, extrapolation from other populations was used as deemed appropriate. The panel also evaluated existing guidelines from other organizations as appropriate when making recommendations. Otherwise, expert opinion and panel consensus was used to form recommendations. These recommendations and their evidence base are discussed below.

Anxiety and Depression

Survivors of cancer are at especially high risk for anxiety and depression because of the multiple stressors, vulnerabilities, and challenges they face. According to the NCCN Guidelines for Distress Management (available online at www.NCCN.org), risk factors for psychosocial distress include cognitive impairment, severe comorbid illnesses, uncontrolled symptoms, communication barriers, or a history of psychiatric disorder, depression, or substance abuse. Social issues, such as living alone, having young children, being of younger age or female, and prior physical or sexual abuse, are also risk factors for psychosocial distress. Anxiety and depression affect up to 29% of survivors, with as many as 19% of survivors reportedly meeting the criteria for post-traumatic stress disorder.[44,47,51-53]

Most commonly, fear of recurrence leads to worry and distress related to surveillance and physical symptoms that may or may not be related to the cancer diagnosis and that can reach levels of clinical anxiety.[11,47,116] Anxiety and/or depression can also occur in survivors secondary to physical compromise, social isolation, or work and financial problems.[44,47,50,117] These challenges are underscored by the inevitable decreased medical and interpersonal support following completion of treatment and transition to the surveillance stage.[114]

Uncontrolled anxiety and/or depression have a significant negative impact on a survivor's quality of life, and sometimes these individuals can develop thoughts of ending their lives. The incidence of completed suicide among patients with cancer and survivors in the United States is about twice that of the general population.[118-122] In addition, survivors with untreated emotional distress are less likely to adhere to recommended surveillance and are less likely to engage in health-promoting activities, such as exercise and smoking cessation.[78]

Management of Anxiety and Depression

Survivors should be screened for anxiety and depression, especially at times of disease transition, surveillance, significant loss, major life events, and social isolation. Treatment recommendations for managing depression and anxiety include routine exercise, which has been shown in clinical trials to have significant effects in reducing symptoms of depression among survivors.[123] In addition to medication treatment, supportive psychotherapy and cognitive behavioral therapy (CBT) are also effective modalities for reducing anxiety and depression in this population.[114,124-128]

For additional information regarding anxiety and depression in patients with cancer, please see the NCCN Guidelines for Distress Management (available at www.NCCN.org). These guidelines may be modified to accommodate the individual circumstances of cancer survivors.

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Anthracycline-Induced Cardiac Toxicity

Many cancer treatments, including chemotherapeutics, targeted agents, and radiation, are associated with cardiovascular toxicities.[129,130] Cardiovascular sequelae can include arrhythmias, pericardial disease, hypertension, thrombosis, cardiomyopathy/heart failure, and vascular and metabolic issues. As a result, a new field focused on the cardiovascular health of patients with cancer and survivors, called "Cardio-Oncology," has become established.[131,132]

Anthracyclines (eg, doxorubicin, epirubicin, daunorubicin) are used to treat many cancer types, including lymphoma, sarcoma, and breast cancer, and are among the best studied and most common causes of cancer treatment-induced cardiac injury.[133] The mechanism by which anthracyclines cause cardiomyopathy is not fully understood, but likely involves the formation of reactive oxygen species (ROS), oxidative injury, and the subsequent induction of apoptosis in cardiac cells.[134] Studies suggest that the incidence of clinical congestive heart failure after anthracycline-based therapy is <5%; however, a significantly higher percentage of patients have evidence of subclinical heart failure with reports of asymptomatic left ventricular ejection fraction (LVEF) decline being 10% to 50% in various studies.[135-137]

The panel focused specifically on anthracycline-induced cardiac toxicity for this version of the guidelines. Other chemotherapies (eg, HER2-targeted agents, angiogenesis inhibitors) may cause cardiomyopathy, and the panel acknowledges that some of the concepts presented in these recommendations may apply to these other cardiomyopathies. However, it is important to note that fewer data are available on the cardiomyopathies associated with non-anthracycline systemic therapies and that these cardiomyopathies may differ in nature from that induced by anthracyclines.[138] More research is needed to understand the specific mechanisms of cardiomyopathies associated with newer agents. In addition, the panel emphasizes that the approach to cardiomyopathy may be different than the approach to other cardiac diseases such as coronary artery disease (CAD), which could occur, for example, as a result of radiation therapy.

Panel Considerations Regarding Anthracycline-Induced Cardiac Toxicity

Anthracycline-induced heart failure may take years or even a decade to manifest. Previous dogma has suggested that anthracycline-induced heart failure portends poor prognosis and is not responsive to therapy. However, emerging data in heart failure due to other types of cardiac injury suggest that signs of cardiac dysfunction can be seen early, prior to the onset of symptoms.[139] Additionally, data from these other types of cardiac injury suggest that early intervention with cardioprotective medications results in better long-term cardiac function.[140,141] Therefore, it is possible that if anthracycline-induced cardiac dysfunction is detected early, it may also be responsive to cardioprotective medications.[138-142] In addition, a growing body of preclinical, observational, and pilot research suggests that lifestyle changes, such as weight control,[143-145] dietary modification (either through correcting dietary deficiencies or increasing intakes of various nutrients),[146] and exercise,[147-149] may also be helpful at these early stages, prior to the onset of heart failure symptoms, although more research is necessary.[150,151]

These emerging issues in anthracycline-induced cardiomyopathy are consistent with the changes in the cardiology community of heart failure at large. Clinical heart failure has established risk factors, and the earliest signs of heart failure begin with the accumulation of these risk factors over time, ultimately resulting in structural cardiac abnormalities and later symptomatic heart failure. As a result, more than a decade

ago, this evolutionary and progressive nature of heart failure was recognized by cardiologists and incorporated into the American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for the Evaluation and Management of Heart Failure.[152] In 2001, the AHA/ACC guidelines proposed a new classification for heart failure.[152] Traditional classifications only recognized heart failure when patients presented with clinical signs and symptoms. The 2001 classification scheme, in contrast, introduced stages of heart failure beginning before the patient is symptomatic, and emphasized the importance of prevention in heart failure management.

The panel believes that this revised AHA/ACC classification is particularly relevant to cardio-oncology populations. Therefore, in formulating the present recommendations for screening, evaluation, and treatment of cardiac dysfunction in survivors who received anthracyclines during their cancer treatment, the panel took into consideration the updated AHA/ACC classification and guidelines for management of heart failure. For these NCCN Guidelines for Survivorship, the panel emphasized early recognition of cardiac toxicity with the goal of preventing the development of clinical, symptomatic heart failure by addressing other known risk factors for heart failure. In particular, appropriate use of cardioprotective medications (such as neurohormonal antagonists [angiotensin-converting enzyme (ACE) inhibitors, beta blockers]) can be considered with the goal of preventing cardiac remodeling over time in some patients. In this respect, the panel emphasizes a thorough clinical screen for heart failure for all survivors with exposure to anthracyclines after completion of therapy, with the additional consideration of an echocardiographic screen in high-risk survivors, as discussed in more detail below. The panel also believes that early involvement of a cardio-oncologist or cardiologist in the care of the cancer survivor is important. For all patients, there should be a low threshold for referral to a cardio-oncologist or cardiologist. In addition, symptoms of heart failure may mimic other conditions such as pulmonary issues and/or cardiac ischemia; therefore, a global approach may be necessary when assessing survivors with decreased cardiorespiratory fitness.[153]

Classification of the Stages of Heart Failure

The revised AHA/ACC classification identifies patients who do not have symptoms associated with heart failure but are either at risk for heart failure (Stage A) or have structural abnormalities of the heart (Stage B).[152] This revised classification has both diagnostic and therapeutic utility, because evidence suggests that treatments prescribed in Stage A (in the absence of structural heart abnormalities or symptoms) can reduce the morbidity and mortality of heart failure in the general population.[138-142] Left untreated, however, the accumulation of risk factors in patients with Stage A heart failure leads to injury or stress on the myocardium and generates a cascade of signaling events in the heart. The subsequent change in the geometry and structure of the left ventricle, often referred to as cardiac remodeling (Stage B), may manifest as cardiac hypertrophy or chamber dilatation. In other cases, the result may be decreased cardiac contractility, which can result in decreased LVEF (also Stage B). Cardiac remodeling generally precedes the development of symptoms (by months or even years), continues after symptoms become evident, and contributes substantially to symptom progression and mortality despite treatment. Individuals are considered to have Stage C heart failure when clinical signs and symptoms accompany structural changes to the heart. Stage D is the most advanced stage, with patients showing advanced structural heart disease and significant heart failure symptoms at rest that are refractory to medical therapy; these patients require specialized interventions.

The panel also considered the New York Heart Association's functional classification of heart failure. [154] In this system, which is based on limitations to physical activity and the effect of physical activity on heart failure symptoms, Stage I is similar to AHA/ACC Stage B, while Stages II and III would be considered AHA/ACC Stage C and Stage IV is similar to AHA/ACC Stage D.

Assessment for Anthracycline-Induced Cardiac Toxicity

The panel recognizes a lack of high-quality data to inform the benefits of screening for heart failure among patients treated with anthracyclines. However, the panel believes that all survivors who have completed anthracycline therapy should undergo a clinical evaluation to assess for signs and symptoms of heart failure. The lack of data is illustrated in a 2007 clinical evidence review by ASCO, which concluded that no studies had systematically addressed the benefits of screening adult cancer survivors with a history of anthracyclines for cardiotoxicity.[129] The review also found no direct evidence showing the effectiveness of cardiac treatment on outcomes of asymptomatic survivors.[129] A 2008 multidisciplinary task force from the Children's Oncology Group came to largely similar conclusions regarding screening for cardiotoxicity in survivors of pediatric cancers.[155] Some reasons for the lack of data on screening survivors for cardiotoxicity have been discussed,[156] and, unfortunately, high-quality data have not been forthcoming since ASCO's review.

In the absence of data, the Children's Oncology Group relied on the collective clinical experience of its panel members and recommended echocardiograms or multiple-gated acquisition (MUGA) scans for survivors of pediatric cancer at the conclusion of treatment and then every 1 to 5 years for life depending on age at treatment, anthracycline dose, and chest irradiation (http://www.survivorshipguidelines.org). Although the frequency of cardiac assessment using echocardiograms or MUGA scans has been a matter of debate, there is general support for at least one assessment in children who have completed anthracycline therapy.[157,158]

A 2014 joint expert consensus statement from the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommends yearly cardiovascular assessment of adult survivors after the completion of potentially cardiotoxic therapy to look for early signs and symptoms of cardiovascular disease, with cardiac imaging used at the discretion of the clinician.[159] The groups recommend echocardiogram as the preferred imaging modality, when imaging is performed. The report also acknowledged the limited data available to inform their recommendations.

The NCCN Survivorship Panel defined its screening recommendations based largely on consensus and on the idea that early recognition and treatment of cardiotoxicity can allow for earlier interventions that may improve prognosis (discussed below).

Assessment for Symptoms of Heart Failure

According to the most recent AHA/ACC guidelines, released in 2013, the cardinal manifestations of clinical heart failure (Stage C) include dyspnea and fatigue (which may lead to limited exercise tolerance) or fluid retention (which may lead to pulmonary and peripheral edema).[160] These symptoms can lead to decreased functional capacity and affect quality of life. Heart failure symptoms associated with fluid retention may also include orthopnea or paroxysmal nocturnal dyspnea. Therefore, the panel recommends a history and physical to look for these symptoms to help identify survivors who might already be symptomatic. These survivors should undergo evaluation with an echocardiogram. If no evidence of structural heart disease is seen, then a workup for other causes of the symptoms is warranted with referral to

other specialties (eg, pulmonology or cardiology) as needed. Symptomatic survivors with evidence of structural heart disease require immediate referral to a cardio-oncologist or cardiologist.

Assessment of Comorbidities and Cardiovascular Risk Factors

The panel recommends assessment of comorbidities and other traditional risk factors for heart disease. Furthermore, the oncologic history of the survivor should be reviewed. Chest radiation can increase the risk of ischemic cardiac disease, which can contribute to heart failure.[130,131] The addition of other cardiotoxic therapies (eg, HER2-targeted agents) to anthracyclines can further increase the risk of heart failure over that seen with the use of anthracyclines alone.[161] Older survivors, those with a higher cumulative anthracycline dose (cumulative doxorubicin dose of 300 mg/m^2 or equivalent), those with underlying cardiovascular disease or risk factors, and those who had a low-normal (50%–54%) baseline ejection fraction are also at increased risk for the development of heart failure.

The panel recognizes the growing body of literature suggesting the possible utility of cardiac biomarkers (specifically troponins) as noninvasive markers of cardiotoxicity. The panel believes that more prospective, multi-institutional studies are needed to make definite recommendations. The optimal timing of troponin assessment in relation to completion of chemotherapy is currently unclear, the cut-off point for a positive test is undefined, and the optimal assay platform remains to be determined. In addition, the sensitivity and specificity of troponin I levels for predicting cardiotoxicity are fairly low, reported at 48% (95% CI, 0.27–0.69) and 73% (95% CI, 0.59–0.84), respectively.[162] A systematic review of the role of post-treatment cardiac troponins as predictive markers of anthracycline-induced left ventricular dysfunction revealed few studies and inconsistent data.[163] The utility of other potential cardiac biomarkers have been reviewed elsewhere.[164]

Imaging

When developing these imaging guidelines for screening for cardiac toxicity in survivors with a history of anthracycline exposure, the panel considered several questions: 1) Is the prevalence of structural heart disease high enough to warrant screening of anthracycline-treated survivors?; 2) Is an abnormal echocardiogram post-anthracycline therapy associated with an increased risk for the future development of symptomatic heart failure?; and 3) Does the recognition of cardiac abnormalities and treatment of cardiac risk factors post-anthracycline therapy affect outcomes?

A study of 53 patients with breast cancer, leukemia, or lymphoma assessed cardiac and vascular function before and 1, 3, and 6 months after anthracycline-based treatment.[135] Subclinical abnormalities of cardiac and vascular function were frequently observed (ie, LVEF fell to <50% in 26% of those whose baseline LVEF was >50%). In the large randomized controlled NSABP B-31 trial, cardiac function was assessed by cardiac imaging in patients after initial anthracycline-based therapy as a requirement for further treatment with trastuzumab.[165] Over 7% of patients experienced cardiac symptoms and/or a decrease in LVEF of >15% after receiving anthracyclines, thus excluding them from being considered for trastuzumab. It is important to note that this was a clinical trial patient population without significant cardiac risk factors or history of cardiac disease. In a non-clinical trial population of patients with cancer, many may already have cardiac risk factors or actual cardiomyopathy prior to treatment, thus elevating the risk of developing heart failure. Together, these results indicate that a significant proportion of survivors with early-onset Stage B or greater heart failure can be identified with appropriate imaging after therapy. However, it is not clear that these declines in LVEF after anthracycline therapy were

associated with an increased risk of developing subsequent heart failure.

Little is known regarding the natural history of heart failure in survivors with Stage B heart failure post-anthracycline therapy, and the long-term prognosis of survivors with cardiac structural abnormalities following anthracycline exposure is not known. However, limited evidence suggests that further remodeling of the heart may be able to be mitigated by initiation of cardioprotective medications. A number of observational and retrospective studies have suggested that early intervention with cardioprotective medication may decrease the rate of cardiac remodeling and progression to heart failure. A randomized controlled trial of 135 survivors of pediatric cancer with ≥1 cardiac abnormality found that the ACE inhibitor enalapril reduced left ventricular end-systolic wall stress compared to placebo (P = .03).[142] The authors concluded that any theoretical benefit of reduced left ventricular end-systolic wall stress must be weighed against the side-effects of treatment; dizziness or hypotension was observed in 22% of the treatment group versus 3% of those receiving placebo (P = .0003), and fatigue was observed in 10% versus 0% (P = .013) of participants. More recently, a review of 247 patients with cancer and declines in LVEF at the Stanford cardiology clinic found that mean LVEF increased after treatment (most often with ACE inhibitors and beta-blockers) and rose to ≥50% in 77% of patients.[141] In addition, a study of 201 adult patients with cancer, who were treated with anthracyclines and had an LVEF of ≤45%, found that earlier initiation of enalapril (and sometimes the beta-blocker carvedilol) was associated with a higher likelihood of LVEF recovery.[139] In the noncancer setting, a randomized controlled trial of >4200 participants found that treatment of patients with asymptomatic left ventricular dysfunction (ejection fraction ≤35%) with enalapril reduced the incidence of heart failure compared with placebo (20.7% vs. 30.2%; P < .001).[140]

Considering these data, the panel believes that survivors with one or more cardiovascular risk factors who have completed anthracycline therapy can be considered for assessment for structural heart disease with appropriate cardiac imaging within 12 months of the last anthracycline dose. Cardiac risk factors to consider include age >65 years, a high cumulative anthracycline dose, underlying cardiovascular disease/risk factors, or a low-normal baseline LVEF.[133]

The panel recommends two-dimensional echocardiogram, coupled with Doppler flow studies, as the cardiac imaging modality of choice when imaging is performed. This technique is widely available and inexpensive, gives no radiation exposure, and is the most useful diagnostic test in the evaluation of patients with possible heart failure.[166,167] It can recognize early stages of heart failure by revealing abnormalities of the pericardium, myocardium, and heart valves.[160] While radionuclide ventriculography (also called radionuclide angiography or MUGA scan) can provide accurate measurements of left ventricular size and function and assessment of ventricular enlargement, it cannot assess valvular abnormalities or cardiac hypertrophy and exposes patients to radiation. Other imaging modalities for the assessment of heart failure have been reviewed elsewhere.[164,166]

Treatment of Anthracycline-Induced Cardiac Toxicity

Progression of heart failure is accelerated with accumulation of risk factors. Injury or stress on the myocardium (such as during and after treatment with anthracyclines) can lead to activation of endogenous neurohormonal systems, which play a critical role in cardiac remodeling and therefore progression to Stage B heart failure.

The panel recommends that heart failure risk factors, including hypertension, obesity, metabolic syndrome, and diabetes, be addressed in all survivors who have completed anthracycline therapy. In addition, survivors with a history of anthracycline therapy should be advised to engage in regular physical activity, eat a healthy diet, and avoid behaviors that may increase the risk of heart failure or cardiovascular disease (eg, tobacco or illicit drug use). Physical activity has been shown to improve control of hypertension and to slow cardiac remodeling in patients with heart failure.[168] Involvement of the survivor's primary care provider in managing risk factors is encouraged.

The panel recommends that a low threshold be established for referral to a cardio-oncologist or cardiologist for all patients previously treated with an anthracycline. Additional recommendations for each stage of heart failure are discussed below.

Treatment of Stage A Heart Failure

Stage A heart failure recognizes several well-established risk factors, each of which contribute to early stages of heart failure. These include hypertension, CAD, diabetes mellitus, a family history of heart failure, or a history of cardiotoxins such as anthracyclines. Therefore, by definition, all survivors with exposure to anthracyclines have Stage A heart failure and should be treated as appropriate. Involvement of the survivor's primary care provider is encouraged.

Treatment of Stages B, C, and D Heart Failure

The panel recommends referral to a cardiologist for all survivors with Stages B, C, or D heart failure. The sooner that treatment is initiated, the more likely it is to be successful.[139]

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Cognitive Dysfunction

Cognitive impairment is a common complaint among cancer survivors and may be a consequence of the tumors themselves or direct effects of cancer-related treatment (eg, radiation therapy). This symptom may be especially prominent in survivors of primary central nervous system (CNS) cancers or those with brain metastases. In addition, survivors who never had brain involvement may also report difficulties in cognition.[169] For some survivors, symptoms persist over the long term.[170] When more severe, the presence of cognitive dysfunction can impact quality of life and function. Cognitive dysfunction is most commonly connected with chemotherapy (sometimes referred to as "chemobrain"), but evidence suggests that therapies other than chemotherapy, such as endocrine therapy and radiation, may be associated with cognitive impairments.[171-177] A recent national cross-sectional study found that a history of cancer is independently associated with a 40% increase of the likelihood of self-reported memory problems.[178]

Cancer-related cognitive changes have primarily been studied in patients with CNS and breast cancer and lymphoma, and those who have undergone hematopoietic stem cell transplant (HSCT), with a wide incidence ranging from 19% to 78%.[170,179-192] Deficits commonly occur in the domains of executive function, learning and memory, attention, and processing speed.[170,191]

Growing evidence supports the patient experience of cognitive dysfunction associated with cancer and its treatment. In one meta-analysis of 17 studies, women treated with chemotherapy for breast cancer 6 or more months previously (n=807) had lower functional abilities than those not treated with chemotherapy (n=291).[182] These deficits were limited to verbal (eg, word-finding) and visuospatial (eg, copying complex images) abilities. However, when compared with their pre-chemotherapy baseline, no differences were noted among patients complaining of cognitive dysfunction. In another study, cognitive function was compared among 196 long-term survivors of breast cancer treated with cyclophosphamide, methotrexate, and fluorouracil (CMF) who were, on average, 21 years out from diagnosis, and 1509 control patients with no a history of cancer.[193] The chemotherapy group did significantly worse on several neuropsychological tests (eg, immediate and delayed verbal memory, executive functioning, psychomotor speed). Finally, one study compared 101 patients who underwent an HSCT with 82 patients treated with a non-myeloablative therapy; both groups showed mild cognitive impairments at baseline.[194] Although no significant differences in cognitive dysfunction were identified at 2-year follow-up, patients who underwent HSCT had poorer performances in several areas, including attention and executive and psychomotor functions.

The correlation between patient reports of cognitive decline and results of neuropsychological testing has not been consistently demonstrated, possibly because of various definitions of cognitive dysfunction and differences in the statistical analyses across studies.[191] However, a recent study of 189 breast cancer survivors found that memory and executive function complaints, present in approximately 20% of the cohort, showed a statistically significant association with results of domain-specific neuropsychological tests.[195]

The underlying mechanisms that might increase the risk for chemotherapy-induced cognitive changes are not known. Studies have reported elevated levels of cytokines or DNA damage as some of the possible mechanisms.[196] Structural studies have supported the hypothesis that neurotoxicity resulting in damage to white matter of the brain may play an important role in cognitive deficits after chemotherapy

treatment.[170,173,181,197,198] In addition, fatigue and depression, common in cancer survivors, may negatively influence cognitive function, although several studies have found that cognitive dysfunction does not correlate with mood.[193,199] Psychosomatic effects can also contribute, as evidenced by a recent study of patients to be treated with chemotherapy, which found that those who were informed of the possible cognitive side effects were more likely to report cognitive dysfunction and perform worse on neuropsychological testing than uninformed patients.[200] A better understanding of the mechanisms that cause cancer-related cognitive impairment is essential for the development of treatments to improve cognitive function and quality of life in patients with cancer and survivors.[169,201,202]

In October 2006, the International Cognition and Cancer Task Force (ICCTF) was formed, comprising a multidisciplinary group of health professionals and health advocates. The mission of ICCTF is to advance understanding of the impact of treatment-related cognitive and behavioral functioning in patients with non-CNS cancers.[203] The group recently published recommendations regarding neuropsychological testing, defining cognitive impairment/changes, and future study design.[202] ICCTF also has a Web site (www.icctf.com) to provide up-to-date information to both physicians and patients seeking assistance in the management of cognitive symptoms associated with cancer treatment.

Assessment and Evaluation for Cognitive Dysfunction

Patients who present with symptoms of cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment, including depression, pain, fatigue, and sleep disturbance. Some medications can also contribute to cognitive impairment. Therefore, current medications, including over-the-counter medications and supplements, should be reviewed. Any potentially contributing factor should be addressed.

For those who present with concomitant focal neurologic deficits and those whose symptoms evolve to include these findings, imaging is indicated to rule out brain or CNS disease. In addition, imaging in the absence of focal findings may be appropriate for patients deemed to be at high risk for recurrence or metastatic disease involving the CNS.

Unfortunately, no effective brief screening tool for cancer-associated cognitive dysfunction in the asymptomatic cancer survivor currently exists. The Mini-Mental State Examination (MMSE[204]) and similar screening tools lack adequate sensitivity to detect a subtle decline in cognitive performance. Instead, the panel listed several questions that can help clarify the nature of the impairment, including inquiries about the ability to pay attention, find words, remember things, think clearly, and perform functions. The time of onset and the trajectory over time should also be assessed.

Neuropsychological evaluation may be helpful when individuals perceive cognitive impairment in a non-specific way and clarity is needed about the nature of impairments to guide rehabilitative efforts. Neuropsychological evaluation itself can be therapeutic and validating. Evaluation may also be necessary if an individual is pursuing disability benefits and cognitive impairment is a contributing factor to work limitation.

Management of Cognitive Dysfunction

Survivors benefit from validation of their symptom experience and should be reassured that, in most patients, cognitive dysfunction does not worsen over time. In fact, data from breast cancer survivors suggest that symptoms may improve over time.[172] The panel recommends the

use of nonpharmacologic interventions whenever possible, with pharmacologic interventions as a last-line of therapy in survivors for whom other interventions have been insufficient, as discussed in the following sections. Additional recommendations for cognitive dysfunction in older adults can be found in the cognitive function section of the NCCN Guidelines for Older Adult Oncology (available at www.NCCN.org).

Nonpharmacologic Interventions for Cognitive Dysfunction

Prospective data are lacking to inform the use or potential benefits of non-pharmacologic interventions for cancer survivors who complain of cognitive dysfunction. In one small study, cognitive behavioral therapy was evaluated in 40 breast cancer survivors using a waitlist control trial design.[205] Although overall quality of life improved with the intervention, statistically significant improvement was noted only with verbal memory, not with self-reports of daily cognitive complaints.

Practical suggestions include instruction in self-management and coping strategies (eg, using planners and reminder notes, keeping items in the same place, minimizing distractions, avoiding multi-tasking), which the panel believes can be very helpful to patients. Discontinuation or limitation of use of medications known to cause or contribute to cognitive impairment should be attempted. Management of distress, pain, sleep disturbances, and fatigue should be provided. In fact, a recent study showed that cognitive behavioral therapy for fatigue was effective at reducing self-reported cognitive disability and concentration problems in 98 severely fatigued cancer survivors.[206] Finally, relaxation, stress management, and routine exercise should all be encouraged. Substantial evidence shows that physical activity enhances cognitive function in elderly people in general, although only few studies specific to cancer survivors have been reported.[207-209]

Occupational therapy strategies focus on improvement of cognitive functioning and may be most effective for individuals who note the impact of specific functional limitations, such as word finding, comprehension, and task completion, on work performance, quality of life, or role expectations.[210]

Pharmacologic Interventions for Cognitive Dysfunction

If nonpharmacologic interventions have been insufficient, consideration of psychostimulants such as methylphenidate or modafinil is reasonable, although data informing the efficacy of these agents are lacking. Trials assessing the effects of methylphenidate have reported mixed results.[211] For example, a randomized, placebo-controlled, double-blind trial found that d-methylphenidate had no effect on neuropsychological test scores.[212] In contrast, a randomized, double-blind, crossover trial of child survivors of acute lymphoblastic leukemia or brain tumors showed that methylphenidate was more effective than placebo at improving attention, cognitive flexibility, and processing speed.[213]

Results of studies on modafinil are more consistent. A randomized controlled trial assessing the efficacy of modafinil for fatigue and cognitive function in breast cancer survivors found significantly greater improvement in memory and attention among patients receiving modafinil than in the placebo group.[214] Similarly, a double-blind, randomized, cross-over trial also in breast cancer survivors found that participants receiving modafinil performed significantly better on cognitive tests of attention and psychomotor speed.[215] Benefits with treatment were also noted among patients with a primary brain tumor.[216]

Fatigue

Note: The Discussion text regarding fatigue in survivors has been adapted from the NCCN Guidelines for Cancer-Related Fatigue (available at www.NCCN.org).

NCCN defines cancer-related fatigue as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[217] Fatigue is a common symptom in patients with cancer and is nearly universal in those receiving cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, or treatment with biological response modifiers.[218-220] According to a survey of 1569 patients with cancer, the symptom is experienced by 80% of individuals who receive chemotherapy and/or radiotherapy.[221,222] Cancer survivors report that fatigue continues to be a disruptive symptom after treatment ends,[223-230] with studies showing that 17% to 29% of cancer survivors experience persistent fatigue for years after the completion of active therapy.[231,232] Persistent cancer related fatigue affects quality of life, because individuals become too tired to fully participate in the roles and activities that make life meaningful.[225,233] Disability related issues are also relevant for cancer survivors, because obtaining or retaining disability benefits from insurers is often difficult for patients with cancer-related fatigue. Identification and management of fatigue remains an unmet need for many cancer survivors.

The specific mechanisms involved in the pathophysiology of cancer-related fatigue are unknown. Proposed mechanisms include pro-inflammatory cytokines, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, circadian rhythm desynchronization, skeletal muscle wasting, and genetic dysregulation.[234-239] Several studies have focused on the cause of fatigue, especially in cancer survivors with no evidence of active disease, and have suggested that persistent immune system activation and chronic inflammatory processes may be involved.[223,240-242] Evidence supporting these mechanisms is limited.

Screening for Fatigue

All survivors should be screened for fatigue to ensure that those with moderate to severe fatigue are identified and treated promptly and effectively. Because fatigue is a subjective experience, clinicians must rely on patients' descriptions of their fatigue level. The panel recommends the use of a severity scale, with survivors being asked, "How would you rate your fatigue on a scale of 0 to 10 over the past 7 days?" Alternately, screening can be performed with patients asked to rate their fatigue as none, mild, moderate, or severe. Scores of 0 to 3 or none to mild fatigue require no further assessment or interventions; these patients should be rescreened at regular intervals. Patients with scores 4 or greater or indicating moderate or severe fatigue should be evaluated further. Studies in patients with cancer have revealed a marked decrease in physical functioning at a reported fatigue level of 7 or higher on the 0 to 10 scale.[243,244]

Evaluation for Moderate to Severe Fatigue

When fatigue is rated as moderate to severe, with a score of 4 to 10, a more focused history and physical examination should be conducted. A thorough history is warranted, because the recommended workup for fatigue differs according to the timing of fatigue onset in relation to the completion of active therapy and the presence of predisposing factors and other symptoms. Fatigue has a variable natural history, with some patients complaining of only mild levels of fatigue even during active therapy and others experiencing severe fatigue for years after treatment completion.

In general, mild to moderate levels of fatigue that persist for 6 to 12 months after the completion of therapy likely do not warrant an extensive workup, unless other symptoms are present. Conversely, when moderate to severe fatigue begins after or worsens during this period, or when other symptoms are present, such as pain, pulmonary complaints, or unintentional weight loss, a more extensive work-up is warranted to screen for the presence of metastatic disease or other comorbidities.

Regardless of fatigue onset, it is always relevant to screen for common contributing factors such as emotional distress, sleep disturbance, pain, and the use of prescriptions or over-the-counter medications or supplements. Possible medical causes of fatigue, including cardiac disease and hypothyroidism, should also be assessed. Disease and treatment considerations also affect recommendations for screening, such as the inclusion of echocardiograms for patients who received cardiotoxic treatments and thyroid screening for patients who received radiation to the neck or thorax.

Management of Fatigue

Several interventions and strategies have been shown to help alleviate fatigue and reduce distress caused by this symptom in patients with cancer and survivors; recommended strategies and interventions are described herein. For additional information about fatigue in survivors and patients with cancer, please see the NCCN Guidelines for Cancer-Related Fatigue (available at www.NCCN.org). The following guidelines may be modified to fit the individual survivor's circumstances.

Treatment of Contributing Factors

Management of fatigue in survivors first includes the treatment of contributing factors such as pain, distress, anemia, and sleep disturbances (more information on treatment of pain, anxiety/depression, and sleep disorders in survivors can be found throughout these guidelines).

Patient and Family Education and Counseling

Education and counseling can be beneficial in helping patients cope with fatigue. Understanding typical patterns of fatigue during and after treatment can help patients set reasonable expectations regarding improvements in energy after the completion of cancer therapy and can help allay concerns that persistent fatigue after the completion of therapy is evidence of disease recurrence. Counseling can help patients develop strategies for self-monitoring of fatigue and techniques such as energy conservation, that may be helpful in the immediate post-treatment period.[245]

Physical Activity

Activity enhancement is a category 1 recommendation. Improving strength, energy, and fitness through regular exercise, even a moderate walking exercise program, has been shown to facilitate the transition from patient to survivor, decrease anxiety and depression, improve body image, and increase tolerance for physical activity. Therefore, survivors with moderate to severe fatigue should be encouraged to maintain adequate levels of physical activity (category 1). Robust data support the efficacy of increased physical activity for reducing fatigue in patients with cancer and survivors.[246-252] A recent meta-analysis of randomized controlled trials found that cancer survivors who participated in exercise interventions, either during or after treatment for cancer, experienced significant improvements in fatigue compared with patients randomized to the control group.[253] Another meta-analysis of 44 studies, including 3254 cancer survivors, concluded that moderate-intensity resistance exercise among older cancer survivors reduced fatigue.[246]

Survivors at a higher risk of injury should be referred to a physical therapist or exercise specialist (also see *Healthy Lifestyles*, below).

Psychosocial Interventions

Psychosocial interventions, such as cognitive behavioral therapy (CBT), psycho-educational therapy, and supportive expressive therapy, including support groups, counseling, and journal writing (all category 1 recommendations), have also been shown to reduce fatigue in cancer survivors, although data are not entirely consistent.[254-259] Several meta-analyses have evaluated the role of psychosocial interventions in reducing fatigue. For example, Kangas et al[258] reported a weighted pooled mean effect of –0.31 for psychosocial interventions on fatigue in an analysis of 3620 patients with cancer from 41 studies. Jacobsen et al[260] analyzed 30 randomized controlled trials and found a significant effect size (dw) for psychological interventions (dw, 0.10; 95% CI, 0.02–0.18), but not for activity-based programs (dw, 0.05; 95% CI, −0.08–0.19). A meta-analysis by Duijts et al[254] reported that, like exercise programs, behavioral techniques, including cognitive therapy, relaxation techniques, counseling, social support, hypnosis, and biofeedback, are beneficial in improving fatigue among patients with breast cancer during and after treatment (standardized mean difference [SMD], -0.16).

Several published studies support the conclusion that CBT interventions designed to optimize sleep quality in patients with cancer may also improve fatigue.[261-264] Two randomized clinical trials of patients who reported chronic insomnia in the survivorship phase demonstrated improvements in both sleep and fatigue after 4 to 5 weekly behavioral therapy sessions.[255,256,265] Two smaller studies of patients with current complaints of insomnia in the survivorship phase reported improved sleep and fatigue.[261,263] Two other studies found positive benefits of a behavioral intervention on sleep and fatigue that were not sustained over time.[264,266] The American Academy of Sleep Medicine (AASM) has recommended 3 specific therapies for chronic insomnia in healthy individuals: relaxation training, cognitive behavior therapy, and stimulus control therapy.[267]

Pharmacologic Interventions

Psychostimulants, such as methylphenidate and modafinil, are also used to treat fatigue, although data regarding their use to treat fatigue in cancer survivors are limited. A 54% response rate to methylphenidate was reported in a phase II trial of 37 breast cancer survivors.[268] A randomized trial in 154 patients post-chemotherapy also found an improvement in fatigue symptoms in the dexmethylphenidate arm.[269] A recent meta-analysis of 5 randomized controlled trials of patients with cancer found limited evidence for the efficacy of 4 or more weeks of methylphenidate treatment for cancer-related fatigue (mean difference, –3.70; 95% CI, –7.03 to –0.37; *P*=.03).[270]

Modafinil also shows some promise for management of post-treatment fatigue in small trials. Morrow et al[271] conducted an open-label study of modafinil for 51 survivors of breast cancer with persistent fatigue. The dose was 200 mg/d for 1 month. A reduction in fatigue was reported among 86% of these survivors. In a pilot study of 30 adults with previously treated brain tumors, modafinil was associated with improvement in fatigue by 8 weeks.[272] Currently, the panel agrees that methylphenidate or modafinil may be considered after ruling out other causes of fatigue, although they acknowledge the limited data supporting the use of these agents in this setting.

Small pilot studies and one recent randomized controlled trial have evaluated the impact of supplements, including ginseng and vitamin D, for cancer-related fatigue.[273] The evidence to date is inconsistent, and the panel currently does not recommend the use of supplements for the treatment of fatigue.

Pain

More than one-third of posttreatment cancer survivors experience chronic pain, which often leads to psychological distress; decreased activity, motivation, and personal interactions; and an overall poor quality of life.[274-278] Pain in survivors is often ineffectively managed. Barriers to optimal pain management in cancer survivors include health care providers' lack of training, fear of side effects and addiction, and reimbursement issues.[279]

Pain has 2 predominant mechanisms of pain: nociceptive and neuropathic.[280,281] Injury to somatic and visceral structures and the resulting activation of nociceptors present in skin, viscera, muscles, and connective tissues cause nociceptive pain. Somatic nociceptive pain is often described as sharp, throbbing, or pressure-like, and often occurs after surgical procedures. Visceral nociceptive pain is often diffuse and described as aching or cramping. Neuropathic pain is caused by injury to the peripheral or central nervous system and might be described as burning, sharp, or shooting. Neuropathic pain often occurs as a side-effect of chemotherapy or radiation therapy or is caused by surgical injury to the nerves.

Screening for and Assessment of Pain

All cancer survivors should be screened for pain at regular intervals. If pain is present, the intensity should be quantified by the survivor. Because pain is inherently subjective, self-report of pain is the current standard of care for assessment. Intensity of pain should be quantified using a 0 to 10 numeric rating scale, a categorical scale, or a pictorial scale (eg, Wong-Baker FACES Pain Rating Scale).[282-285] In addition, the survivor should be asked to describe the characteristics of the pain (eg, aching, burning). Severe uncontrolled pain is a medical emergency and should be responded to promptly. In addition, a oncologic emergency should also be ruled out in these cases.

A comprehensive evaluation, as outlined in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org), is essential to ensure proper pain management. The cause and pathophysiology of the pain should be identified to determine the optimal therapeutic strategy. In addition, the survivor's goals for comfort and function should be determined.

Management of Pain

The goals of pain management are to increase comfort, maximize function, and improve quality of life. A multidisciplinary approach is recommended, with a combination of pharmacologic treatments, psychosocial and behavioral interventions, physical therapy and exercise, and interventional procedures.[275,286,287]

The NCCN Survivorship Panel made recommendations for the management of 8 categories of cancer pain syndromes: neuropathic pain, chronic postoperative pain (ie, pain syndromes after amputation, neck dissection, mastectomy), myalgias/arthralgias, skeletal pain, myofascial pain, gastrointestinal/urinary/pelvic pain, lymphedema, and postradiation pain. Neuropathic pain commonly results from some systemic anticancer agents.[274] The incidence of chronic pain after surgical treatment varies with the type of procedure and is as high as 60% in patients treated with breast surgery and 50% in those treated with lung surgery.[274] Arthralgias, characterized by joint pain and stiffness, occur in roughly half of women taking aromatase inhibitors as adjuvant therapy for breast cancer.[288] Pelvic pain often occurs after pelvic radiation, resulting from fractures, fistulae, proctitis, cystitis, dyspareunia, or enteritis.[274]

Pharmacologic interventions, local therapies, psychosocial support and behavioral treatments, physical therapy and exercise, and interventional procedures are discussed below. For more information about the

management of cancer-related pain, please see the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org). These guidelines include information on opioid use and pain treatment agreements for patients at risk for medication misuse or diversion; adjuvant analgesics; and psychosocial support and behavioral interventions that may be modified to fit the individual survivor's circumstances.

Pharmacologic Interventions

Pharmacologic measures are the foundation of treatment of many of the common pain syndromes in survivors. Pharmacologic recommendations in these guidelines vary depending on the pain syndrome and include opioids, adjuvant analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and muscle relaxants.[275,289-291] Topical medications are discussed in *Local Therapies*, below.

Opioids: Opioids may be recommended for the treatment of neuropathic, postoperative, and skeletal pain. Data on the long-term use of opioids in survivors are lacking.[287,290,292]

The NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org) recommend screening survivors for risk factors of aberrant opioid use or diversion of pain medication, using a detailed patient evaluation and/or tools such as the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) or Opioid Risk Tool (ORT) before prescribing.[293-297] In addition, if opioids are deemed necessary for any survivor (regardless of aberrant use risk level), the NCCN Survivorship Panel recommends using the lowest dose possible and reevaluating the effectiveness and necessity of opioids on a regular basis. Pain treatment agreements can also be considered.[298]

Adjuvant Analgesics: Adjuvant analgesics include antidepressants (eg, serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants), anticonvulsants (eg, gabapentin, pregabalin), and corticosteroids. These are recommended for the treatment of neuropathic and postoperative pain and for myalgias and arthralgias in survivors. The term adjuvant refers to the fact that they are often coadministered with an opioid to enhance analgesia or reduce the opioid requirement, but they may also be used as the sole pain treatment. A recent systematic review found that antidepressants, anticonvulsants, other adjuvant analgesics, and opioids were all effective at reducing neuropathic pain in patients with cancer.[290] Another review found that antidepressants and antiepileptics provide additional neuropathic pain relief when added to opioids in patients with cancer.[299]

Tricyclic antidepressants have been shown to relieve neuropathic pain in the noncancer setting.[300,301] In addition, the SNRI duloxetine was recently shown to effectively reduce pain in a multi-institutional, randomized, double-blind, placebo-controlled, crossover trial of 231 patients with painful chemotherapy-induced neuropathy.[302]

The most commonly used anticonvulsant drugs for the treatment of cancer-related pain, gabapentin and pregabalin, have primarily been studied in noncancer neuropathy syndromes.[303,304] Only limited data support the effectiveness of corticosteroids for cancer-related pain, and they may also have anti-inflammatory effects.[305-307]

Nonsteroidal Anti-Inflammatory Drugs: NSAIDs are recommended for the treatment of myofascial and skeletal pain and for myalgias and arthralgias. NSAIDs are nonopioid analgesics that block the biosynthesis of prostaglandins, which are inflammatory mediators that initiate, cause, intensify, or maintain pain. A recent systematic review found that data supporting the use of NSAIDs for control of pain in patients with advanced cancer are limited and weak, but suggest some efficacy at reducing pain and opioid dose requirement.[308]

A discussion of contraindications and safety precautions that should be considered before prescribing NSAIDs is provided in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org).

Muscle Relaxants: Muscle relaxants (eg, diazepam, lorazepam, metaxalone) reduce muscle spasm and are recommended for the treatment of skeletal pain, myalgias, and arthralgias. Evidence for their efficacy in providing pain relief in the noncancer settings is limited.[309,310] No data could be found in the setting of cancer-related pain.

Psychosocial Support and Behavioral Interventions

Cognitive interventions are aimed at enhancing a sense of control over the pain or its underlying cause. Breathing exercises, relaxation, imagery or hypnosis, and other behavioral therapies can be very useful.[276,311-316] Psychosocial support and education should also be provided.[317] Some studies in patients with cancer suggest that psychosocial and behavioral interventions such as skills training, education, relaxation training, supportive–expressive therapy, and cognitive-behavioral therapy may be effective at reducing pain.[313,318] Hypnosis can also be considered for treatment of neuropathic pain. Overall, data support the benefit of hypnosis for controlling pain in cancer and other settings, but are lacking in the survivorship population.[319]

In general, studies regarding psychosocial support and behavioral interventions for reducing pain in survivors are limited. A recent systematic review and meta-analysis assessed the efficacy of psychosocial interventions for treating pain in patients with breast cancer and survivors.[320] Although results suggest an effect, more studies are clearly needed in the survivorship population.

Physical Therapy and Exercise

Physical therapy and general exercise may also be effective for the treatment of pain in survivors, with the main goal of increasing mobility.[248,276,286,321] Several randomized controlled trials have reported a reduction of neck and shoulder pain associated with exercise or therapy programs.[322-324] In one study, 52 survivors of head and neck cancer were randomized to a progressive resistance exercise training (PRET) program or standard therapeutic exercise for 12 weeks.[324] Pain scores decreased more dramatically in the PRET group (P = .001). In another study of 66 survivors of breast cancer, those randomized to an 8-week water exercise program experienced a greater reduction of neck and shoulder pain than those randomized to usual care.[322] In addition, group exercise in the community with trainers specifically trained to work with cancer survivors has been shown to reduce pain and other symptoms.[325]

Local Therapies

Local therapies, including heat, cold packs, massage, medicated creams, ointments, and patches, are recommended for the treatment of myalgias, arthralgias, and neuropathic and myofascial pain.[276] Specifically, topical lidocaine, capsaicin, ketamine, and amitriptyline are recommended for treatment of some of the various cancer pain syndromes. Data are limited on the effectiveness of ketamine and amitriptyline,[326-331] but the evidence for the effectiveness of lidocaine and capsaicin is stronger.[326,328-330] In a randomized trial of 35 patients with non–cancer-related postherpetic, postoperative, or diabetes-related neuropathic pain, pain intensity was reduced with topical lidocaine but not with topical amitriptyline when compared with placebo.[329] A larger trial with a similar population of 92 patients found no effect of topical amitriptyline, ketamine, or a combination of the two.[332] Another study found that a higher dose of amitriptyline had some efficacy in reducing

peripheral neuropathy, but also showed systemic effects.[333] Lidocaine has been shown to reduce the severity of postherpetic neuropathy and cancer-related pain.[334,335]

Interventional Procedures

Referral to pain management services for interventional procedures, including transcutaneous electrical nerve stimulation (TENS), intercostal nerve blocks, and dorsal column stimulation, is recommended for refractory pain in survivors. Data on the efficacy of these interventions are mainly from patients with active cancer or from the noncancer setting.[276,336] TENS is a noninvasive procedure with electrodes placed in or around the painful area.[276] A recent systematic review found that data supporting the efficacy of TENS for reducing cancer-related pain are inconclusive.[337] The goal of invasive interventions, such as an intercostal nerve block, is to interrupt nerve conduction by either destroying nerves or interfering with their function.[276] The data on these interventions are also limited.[276]

Acupuncture

Acupuncture is recommended as an option for the treatment of myofascial pain in survivors. Evidence supporting the efficacy of this technique for reducing cancer-related pain is extremely limited.[338,339]

Sexual Dysfunction

Cancer treatment, especially hormonal therapy and therapy directed towards the pelvis, can often impair sexual function. In addition, depression and anxiety, which are common in survivors, can contribute to sexual problems. Thus, sexual dysfunction is common in survivors and can cause increased distress and have a significant negative impact on quality of life.[340-344] Nonetheless, sexual function is often not discussed with survivors.[345-347] Reasons for this include a lack of training of health care professionals, discomfort of providers with the topic, and insufficient time during visits for discussion.[340] However, effective strategies for treating both female and male sexual dysfunction exist,[348-351] making these discussions a critical part of survivorship care.

Female Aspects of Sexual Dysfunction

Female sexual problems relate to issues such as sexual desire and arousal, orgasm, and pain.[352-354] Sexual dysfunction after cancer treatment is common in female survivors.[19,343,355-360] A survey of 221 survivors of vaginal and cervical cancer found that the prevalence of sexual problems was significantly higher among survivors than among age- and race-matched controls from the National Health and Social Life Survey (mean number of problems 2.6 vs 1.1; $P<.001$).[359] A survey of survivors of ovarian germ cell tumors and age-and race- and education-matched controls found that survivors reported a significant decrease in sexual pleasure.[361]

Female sexual dysfunction varies with cancer site and treatment modalities.[356,357] For example, survivors of cervical cancer who were treated with radiotherapy had worse sexual functioning scores (for arousal, lubrication, orgasm, pain, and satisfaction) than those treated with surgery, whose sexual functioning was similar to that of age- and race-matched noncancer controls.[356] A recent systematic review of sexual functioning in cervical cancer survivors found similar results, except that no differences in orgasm/satisfaction were observed.[362] In contrast, chemotherapy seems to be linked to female sexual dysfunction in breast cancer survivors,[357] possibly related to the prevalence of chemotherapy-induced menopause in this population.[353] In addition, survivors with a history of hematopoietic stem cell transplantation (HSCT) may have multiple types of sexual dysfunction even after 5 to 10 years.[363-365] Some of the sexual dysfunction associated with HSCT is related to graft–versus-host disease (GVHD), which can result in vaginal fibrosis, stenosis, mucosal changes, vaginal

irritation, bleeding, and increased sensitivity of genital tissues.[364,366] In addition, high-dose corticosteroids use for chronic GVHD can increase emotional lability and depression, affecting feelings of attractiveness, sexual activity, and quality of sexual life.

Evaluation and Assessment for Female Sexual Function

At regular intervals, female cancer survivors should be asked about their sexual function, including their sexual functioning before cancer treatment, their present activity, and how cancer treatment has impacted their sexual functioning and intimacy. The age and relationship status of the survivor may also affect sexual functioning (ie, some women may not be sexually active because of the physical health of their partner or quality of their relationship). The Brief Sexual Symptom Checklist for Women can be used as a primary screening tool.[367] Inquiries into treatment-related infertility should be made if indicated, with referrals as appropriate. ASCO's recently updated clinical practice guidelines on fertility preservation for patients with cancer have more information on the topic.[368] It is important for providers to be aware that fertility issues can be addressed in the survivorship phase, even if they were not addressed prior to treatment.[369]

Patients with concerns about their sexual function should undergo a more thorough evaluation, including screening for possible symptoms and psychosocial problems (ie, anxiety, depression, relationship issues, body image concerns, drug or alcohol use) that can contribute to sexual dysfunction. It is also important to identify prescription and over-the-counter medications (especially hormone therapy, narcotics, and serotonin reuptake receptor inhibitors [SSRIs]) that could be a contributing factor. Traditional risk factors for sexual dysfunction, such as cardiovascular disease, diabetes, obesity, smoking, and alcohol abuse, should also be assessed, as should the patient's oncologic and treatment history. If anti-cancer treatments have resulted in menopause, menopausal symptoms and effects on sexual function should be assessed. Risks and benefits of hormone therapy should be considered in women who have not had hormone-sensitive cancers and who are prematurely post-menopausal. In addition, a physical examination should be performed or referral for gynecologic examination be made to note points of tenderness, vaginal atrophy, and anatomic changes associated with cancer and cancer treatment.

For a more in-depth evaluation of sexual dysfunction, the Female Sexual Function Index (FSFI[370]) and/or the PROMIS Sexual Function Instrument[371] can be considered. The FSFI instrument has been validated in patients with cancer and cancer survivors.[372,373] The PROMIS tool has been validated in a mixed group of patients that included those undergoing active treatment and those post-treatment.[371]

Interventions for Female Sexual Dysfunction

Female sexual dysfunction is often multifactorial in nature. Therefore, treatment of sexual dysfunction often requires a multidimensional treatment plan that addresses the underlying issues, which can be physiologic (ex, menopause, illness), disease-induced, medication-induced, psychologic (ex, anxiety, depression), and interpersonal.

Overall, the evidence base for interventions to treat female sexual dysfunction in survivors is weak and high-quality studies are needed.[374,375] Based on evidence from other populations, evidence from survivors when available, recommendations from the American College of Obstetricians and Gynecologists (ACOG),[352] and consensus among NCCN Survivorship Panel members, the panel made recommendations for treatment of female sexual dysfunction in survivors. The panel recommends that treatment be guided by the specific type of problem. The evidence base for each recommendation is described herein.

Water-, oil-, or silicone-based lubricants, vaginal moisturizers, and topical lidocaine can help alleviate symptoms such as vaginal dryness and sexual pain.[376] In one study of breast cancer survivors, the control group used a non-hormonal moisturizer and saw a transient improvement in vaginal symptoms.[377]

Pelvic floor muscle training may improve sexual pain, arousal, lubrication, orgasm, and satisfaction. A small study of 34 survivors of gynecologic cancers found that pelvic floor training significantly improved sexual function.[378]

Vaginal dilators are recommended for vaginismus, sexual aversion disorder, vaginal scarring, or vaginal stenosis from pelvic surgery or radiation and associated with GVHD. However, evidence for the effectiveness of dilators is limited.[379]

Vaginal estrogen (pills, rings, or creams) has been shown to be effective in treating vaginal dryness, itching, discomfort, and painful intercourse in postmenopausal women.[380-385] Small studies have looked at different formulations of local estrogen, but data assessing the safety of vaginal estrogen in survivors are limited.

The FDA recently approved the selective estrogen receptor modulator ospemifene for treating moderate to severe dyspareunia in postmenopausal women without known or suspected breast cancer and without a history of breast cancer.[386] Ospemifene has been studied in several large trials of women with postmenopausal vulvar and vaginal atrophy and was found to effectively treat vaginal dryness and dyspareunia.[387-389] No data in the survivorship population are available. The panel recommends consideration of ospemifene for dyspareunia in survivors, but only if the patient's cancer was not hormonally sensitive.

Psychotherapy may be helpful for women experiencing sexual dysfunction, although evidence on efficacy is limited.[390] Options include cognitive behavior therapy (CBT), for which some evidence of efficacy exists in survivors of breast, endometrial, and cervical cancer.[391,392] Referrals for psychotherapy, sexual/couples counseling, or gynecologic care should be given as appropriate, and ongoing partner communication should be encouraged.[393] A multidisciplinary treatment plan can be very helpful in situations where psychosocial dysfunction is contributing to sexual dysfunction.

Currently, the panel does not recommend the use of oral phosphodiesterase type 5 inhibitors (PDE5i) for female sexual dysfunction because of the lack of data regarding their effectiveness in women. Although thought to increase pelvic blood flow to the clitoris and vagina,[394,395] PDE5i showed contradictory results in randomized clinical trials of various non-cancer populations of women being treated for sexual arousal disorder.[396-401] More research is needed before a recommendation can be made regarding the use of sildenafil for the treatment of female sexual dysfunction.

Male Aspects of Sexual Dysfunction

The NIH Consensus Conference on Impotence defined impotence as "male erectile dysfunction, that is, the inability to achieve or maintain an erection sufficient for satisfactory sexual performance."[402] In fact, impotence and erectile dysfunction (ED) are not synonymous. Impotence can involve problems of sexual desire, orgasm, or ejaculation, which are not necessarily linked with achieving or maintaining an erection.[403]

ED occurs frequently in the general population and increases with age.[404] In one community-based study, 33% of men aged at least 75 years reported moderate or worse ED.[405] ED is also very common in

male cancer survivors. Anticancer treatment modalities used in a variety of cancers have the potential to damage blood vessels, leading to a reduction in blood circulation to the penis and/or damage to the autonomic nervous system. Thus higher rates of ED are seen in cancer survivors than in the general population. The prevalence of ED in male survivors of colorectal cancer has been reported to range from 45% to 75%,[341,406,407] and it has been reported in up to 90% of survivors of prostate cancer.[408-412]

In 2005, the American Urological Association (AUA) published a guideline on the management of ED; it was reviewed and confirmed as still valid by the AUA in 2011.[403] Using a consensus-based approach with the AUA guideline as a guide, the NCCN Survivorship Panel concluded that: 1) informed patient and physician decision-making is the standard for guiding treatment decisions for ED treatment; and 2) a psychological overlay frequently exists in patients with ED and may be even more pronounced in the face of cancer survivorship. Endocrine disorders are also an important consideration in the cause of ED. Although sex therapy and the diagnosis and treatment of endocrine disorders are important management issues, these are beyond the scope of these guidelines and are therefore not addressed in depth.

Evaluation and Assessment for Male Sexual Function

Male cancer survivors should be asked about their sexual function at regular intervals. Patients should be asked about their sexual functioning before they received the cancer diagnosis and their perceptions regarding the impact of cancer treatment on their sexual functioning and intimacy. A quantitative questionnaire, such as the Sexual Health Inventory for Men (SHIM), can be considered to help identify patients who might benefit from treatment of ED.[404]

Patients with concerns about their sexual function should undergo a more thorough evaluation, including screening for possible psychosocial problems (ie, anxiety, depression, relationship issues, drug or alcohol use) that can contribute to sexual dysfunction. Identifying prescription and over-the-counter medications (especially hormone therapy or opioids) that could be a contributing factor is also important. A focused physical examination can also be helpful and should include examination of the chest (for gynecomastia), abdomen, phallus, scrotum/testicles, and cord structures.

Importantly, cardiovascular risk should be estimated for all men with ED, especially those with cardiovascular disease. Cardiovascular disease and ED share risk factors and often coexist.[413] Sexual activity is considered equivalent to walking 1 mile in 20 minutes on a flat surface or to climbing 2 flights of stairs in 20 seconds.[413] Men who cannot perform these exercises without symptoms are considered to be at high risk for adverse events associated with sexual activity and should be referred to a cardiologist before treatment for ED.[413]

Interventions for Male Sexual Dysfunction

Treatment for ED begins with modification of risk factors, such as smoking cessation, weight loss, increasing physical activity, and avoiding excess alcohol consumption. In addition, treatment of psychosocial problems, with referral to sex and couples therapy as appropriate, can often alleviate symptoms of ED.

Oral phosphodiesterase type 5 inhibitors (PDE5i) have been shown to improve the symptoms of ED and be well tolerated.[348,350] Many studies have also shown the efficacy and tolerability of PDE5i for treating ED in patients with cancer and survivors.[414,415] Importantly, PDE5i are contraindicated in patients taking oral nitrates, because together they can lead to a dangerous decrease in blood pressure.[416,417]

The timing and dose of PDE5i should be started conservatively, and it should be titrated to maximum dose if needed.[403] The patient should be monitored periodically for efficacy, side effects, and any significant change in health status. An adequate trial of PDE5i is defined as at least 5 separate occasions at the maximum dose before reporting it as noneffective, unless the reason for fewer trials is an unacceptable side effect. A different PDE5i can be tried after failure of first-line PDE5i therapy.

If the second PDE5i fails, additional interventions can be considered, with referral to a urologist. These options include second-level interventions such as intraurethral alprostadil suppositories, intracavernous vasoactive drug injection therapy, and vacuum constriction devices (VCDs). A third level and definitive type of intervention, penile prosthesis implantation, can be considered.[403]

Sleep Disorders

Sleep disturbances include insomnia (trouble falling or staying asleep resulting in daytime dysfunction), excessive sleepiness (which can result from insufficient sleep opportunity, insomnia, or other sleep disorders), sleep-related movement or breathing disorders, and parasomnias.[418] Sleep disorders affect 30% to 50% of patients with cancer and survivors, often in combination with fatigue, anxiety, or depression.[418-427] Improvements in sleep lead to improvements in fatigue, mood, and quality of life.[265] Most clinicians, however, do not know how best to evaluate and treat sleep disorders.[418]

Sleep disorders are common in patients with cancer as a result of multiple factors, including biologic changes, the stress of diagnosis and treatment, and side effects of therapy (eg, pain, fatigue).[428] In addition, evidence suggests that changes in inflammatory processes from cancer and its treatment play a role in sleep disorders. These sleep disturbances can be perpetuated in the survivorship phase by chronic side effects, anxiety, depression, medications, and maladaptive behaviors such as shifting sleep times, excessive time in bed because of fatigue, and unplanned naps.[428]

Additional information about sleep disorders in patients with cancer can be found in the NCCN Guidelines for Palliative Care and the NCCN Guidelines for Cancer-Related Fatigue (available at www.NCCN.org). These guidelines may be modified to fit the individual survivor's circumstances.

Screening for and Assessment of Sleep Disorders

Survivors should be screened for possible sleep disorders at regular intervals, especially when they experience a change in clinical status or treatment. The panel lists screening questions that can help determine whether concerns about sleep disorders or disturbances warrant further assessment. Other tools to screen for sleep problems have been validated.[429,430]

If concerns regarding sleep are significant, the panel recommends that treatable contributing factors be assessed and managed. Comorbidities that can contribute to sleep problems include alcohol and substance abuse, obesity, cardiac dysfunction, endocrine dysfunction, anemia, neurologic disorders, pain, fatigue, and emotional distress. In addition, some medications, both prescription and over-the-counter, can contribute to sleep issues. For instance, pain medication, antiemetics, and antihistamines can all contribute to sleep disturbance, as can the persistent use of sleep aids.

Diagnosis of Sleep Disorders

The panel divided sleep disorders into 2 general categories: 1) insomnia and 2) sleep disturbance and/or excessive sleepiness.

Insomnia is diagnosed when patients have difficulty falling asleep and/or maintaining sleep at least 3 times per week for at least 4 weeks, accompanied by distress.

Diagnosing patients with excessive sleepiness can be challenging, because it can be caused by a variety of factors. When excessive sleepiness is associated with observed apneas or snoring, the STOP questionnaire can be used as a screening tool to determine the risk of obstructive sleep apnea (OSA).[431] Other screening tools for OSA risk have also been validated.[432] Sleep studies (ie, laboratory polysomnography [PSG] or home sleep studies) can confirm the diagnosis of OSA. Multiple sleep latency tests (MSLT) and PSG can also be useful in diagnosing narcolepsy, idiopathic hypersomnia, and parasomnias. Narcolepsy should be considered when excessive sleepiness is accompanied by cataplexy, frequent short naps, vivid dreams, disrupted sleep, or sleep paralysis.

Excessive sleepiness can also be associated with uncomfortable sensations or an urge to move the legs (and sometimes the arms or other body parts). These symptoms are usually worse at night and with inactivity, may be improved or relieved with movement such as walking or stretching, and indicate restless leg syndrome (RLS, also known as Willis-Ekbom disease). In these individuals, ferritin levels should be checked; levels less than 45 to 50 ng/mL indicate a treatable cause of RLS.[433,434]

Management of Sleep Disorders

OSA should be treated with continuous positive airway pressure (CPAP), surgery, and/or oral appliances.[435-437] Additionally, weight loss and exercise should be recommended, and survivors should be referred to a sleep specialist.

RLS is treated with dopamine agonists, benzodiazepines, gabapentin, and/or opioids, and referral to a sleep specialist.[438-446] Two separate recent meta-analyses found dopamine agonists and calcium channel alpha-2-delta ligands (eg, gabapentin) to be helpful for reducing RLS symptoms and improving sleep in the noncancer setting.[446,447]

For other types of sleep disturbances, several types of interventions are recommended, as described below.[267,418,448] In addition, referral to a sleep specialist can be considered in most cases.

Sleep Hygiene Education: Educating survivors about general sleep hygiene is recommended, especially for the treatment of insomnia.[449-451] Key points are listed in the guidelines and include regular morning or afternoon exercise; daytime exposure to bright light; keeping the sleep environment dark, quiet, and comfortable; and avoiding heavy meals, alcohol, and nicotine near bedtime.

Physical Activity: Physical activity may improve sleep in patients with cancer and survivors.[248,452-457] One recent randomized controlled trial compared a standardized yoga intervention plus standard care with standard care alone in 410 survivors (75% breast cancer; 96% women) with moderate to severe sleep disruption.[454] Participants in the yoga arm experienced greater improvements in global and subjective sleep quality, daytime functioning, and sleep efficiency (all $P \leq .05$). In addition, the use of sleep medication declined in the intervention arm ($P \leq .05$).

A recent meta-analysis of randomized controlled trials in patients who had completed active cancer treatment showed that exercise improved sleep at a 12-week follow-up.[248] Overall, however, data supporting improvement in sleep with physical activity are limited in the survivorship population.

Psychosocial Interventions: Psychosocial interventions such as cognitive behavioral therapy (CBT), psychoeducational therapy, and supportive expressive therapy are recommended to treat sleep disturbances in survivors.[458] In particular, several randomized controlled trials have shown that CBT improves sleep in the survivor population.[255-257,264] For example, a randomized controlled trial in 150 survivors (58% breast cancer; 23% prostate cancer; 16% bowel cancer; 69% women) found that a series of 5 weekly group CBT sessions was associated with a reduction in mean wakefulness of almost 1 hour per night, whereas usual care (in which physicians could treat insomnia as they would in normal clinical practice) had no effect on wakefulness.[255]

In addition, a small randomized controlled trial of 57 survivors (54% breast cancer; 75% women) found that mind–body interventions (mindfulness meditation or mind-body bridging), decreased sleep disturbance more than sleep hygiene education did.[459]

Pharmacologic Interventions: Many pharmacologic treatments for sleep disturbances are available, including psychostimulants for narcolepsy (eg, modafinil, methylphenidate) and hypnotics for insomnia (eg, zolpidem, ramelteon).[448,460,461] In addition, antidepressants, antihistamines, antiepileptics, and antipsychotics are often used off-label for the treatment of insomnia, even though limited to no efficacy or effectiveness data are available for this use. The panel also noted that these medications are associated with significant risks and should be used with caution. One small, open-label study found that the antidepressant mirtazapine increased the total amount of nighttime sleep in patients with cancer.[462] Overall, however, data on pharmacologic interventions aimed at improving sleep in patients with cancer and survivors are lacking.[427]

Continued on next page.

Recommendations for Preventive Health

Analysis of data from the Behavioral Risk Factor Surveillance System (BRFSS) indicates that a large proportion of cancer survivors have significant comorbidities, smoke, are obese, and/or do not engage in physical activity.[463] Analysis of data from other studies, including the National Health Interview Survey, showed similar results.[464,465] A survey by the American Cancer Society found that 9.3% of long-term survivors smoke.[466]

In addition, many survivors forego recommended cancer screenings (ie, colorectal and cervical screening) and follow-up surveillance[467-469] or demand more intense surveillance than evidence supports.[61]

Healthy Lifestyles

Healthy lifestyle habits, such as engaging in routine physical activity, maintaining a healthy diet and weight, and avoiding tobacco use, have been associated with improved health outcomes and quality of life. For some cancers, a healthy lifestyle has been associated with a reduced risk of recurrence and death.[470-475] Therefore, survivors should be encouraged to achieve and maintain a healthy lifestyle, including attention to weight management, physical activity, and dietary habits. Survivors should be advised to limit alcohol intake and avoid tobacco products, with emphasis on tobacco cessation if the survivor is a current smoker or user of smokeless tobacco. Clinicians should also advise survivors to practice sun safety habits as appropriate, such as using a broad-spectrum sunscreen, avoiding peak sun hours, and using physical barriers. Finally, survivors should be encouraged to see a PCP regularly and adhere to age-appropriate health screenings, preventive measures (eg, immunizations), and cancer screening recommendations.

The panel made specific recommendations regarding physical activity, weight management, nutrition, and supplement use, which are discussed herein. Although achieving all of these healthy lifestyle goals may be difficult for many survivors, even small reductions in weight among overweight or obese survivors or small increases in physical activity among sedentary individuals are thought to yield meaningful improvements in cancer-specific outcomes and overall health.[476]

Physical Activity

During cancer treatment, many survivors become deconditioned and can develop impaired cardiovascular fitness because of the direct and secondary effects of therapy.[477] Randomized trials have shown that exercise training is safe, tolerable, and effective for most survivors. Structured aerobic and resistance training programs after treatment can improve cardiovascular fitness and strength and can have positive effects on balance, body composition, and quality of life.[246,248,252,478-484] The effectiveness of exercise training is especially well studied in women with early-stage breast cancer. Survivors of breast cancer who exercise have improved cardiovascular fitness and therefore an increased capacity to perform daily life functions, resulting in a better quality of life.[247,250,252,484,485] Furthermore, a recent study of adult survivors of childhood Hodgkin lymphoma found that vigorous exercise was associated with a reduction in the risk of major cardiovascular events after a median follow-up of 11.9 years.[486] In fact, the finding was dose-dependent, and survivors who reported ≥9 MET hours/week experienced a 51% reduction in risk compared with those reporting <9 MET hours/week (P = .002).

In addition, observational studies have consistently found that physical activity is linked to decreased cancer incidence and recurrence and increased survival for certain tumor types.[482,487-496] For example, one meta-analysis of 6 studies including more than 12,000 survivors of

breast cancer found that post-diagnosis physical activity reduced all-cause mortality by 41% ($P < .00001$) and disease recurrence by 24% ($P = .00001$).[490] Data from other meta-analyses primarily consisting of observational studies of survivors of colorectal, ovarian, non-small cell lung, brain, prostate, and breast cancers show that physical activity is associated with decreased all-cause mortality and/or cancer-specific mortality.[488,491,495,497] In fact, analyses of data from 986 survivors of breast cancer from the National Runners' and Walkers' Health Studies found that mortality decreased with increased rates of energy expenditure.[496] Evidence in other disease sites is less robust, but also suggests survival benefits associated with exercise in survivors after treatment.[497]

Data also support the idea that inactivity/sedentary behavior is a risk factor for cancer incidence and mortality and impacts mood and quality of life in survivors, independent of the level of an individual's recreational or occupational physical activity.[470,498-502] For example, in a cohort of more than 2000 survivors of nonmetastatic colorectal cancer, those who spent more leisure time sitting had a higher mortality than those who spent more time in recreational activity.[470]

Evaluation and Assessment for Physical Activity

Survivors should be asked about readiness for participation and their current level of physical activity at regular intervals. The Godin Leisure-Time Exercise Questionnaire is one tool that can be used to assess a survivor's exercise behavior, with a modified version also able to assess daily time in moderate-to-vigorous activity.[503,504]

For survivors who are not meeting the guideline recommendations (see later discussion), barriers to physical activity should be discussed and addressed, if possible. Common barriers include not having enough time to exercise, not having access to an acceptable exercise environment, uncertainty about safety of exercise post-treatment, lack of knowledge regarding appropriate activities, and physical limitations.[505] In addition, alleviation of pain, fatigue, distress, or nutritional deficits can facilitate the initiation of an exercise program.

Risk Assessment for Exercise-Induced Adverse Events

Exercise is considered safe for most survivors.[252,484,506] However, a significant portion of survivors may have comorbid conditions or risk factors that make them unable to safely exercise without trained supervision.[507] Therefore, a risk assessment is required for all survivors before prescribing a specific exercise program.[484,508] The type of cancer, treatment modalities received, and the number and severity of comorbidities determine risk levels.[506] Thus, disease and treatment history, late and long-term effects, and comorbidities should be assessed. A standardized pre-participation screening questionnaire, such as the The Physical Activity Readiness Questionnaire for Everyone (PAR-Q+),[509] can also be considered to identify patients for whom unsupervised physical activity is likely safe versus those for whom it may pose undue risk.

Survivors with myeloma, peripheral neuropathy, poor bone health, arthritis, or musculoskeletal issues are considered at moderate risk for exercise-induced adverse events. Stability, balance, and gait should be assessed in survivors with peripheral neuropathy before they engage in exercise, and exercise choice should be made based on the results (ie, stationary bike or water aerobics for survivors with poor balance). Survivors with osteoporosis or bone metastases should have fracture risk and/or bone density assessed as clinically indicated before initiating an exercise program. Moderate-risk survivors can often follow the general recommendations for physical activity; however, medical clearance and/or referrals to trained personnel such as a physical therapist, certified trainer, cancer rehabilitation specialist, pulmonary or cardiac rehabilitation specialist, or exercise specialist can also be

considered. Specialized training in cancer exercise is available through the American College of Sports Medicine (ACSM; http://www.acsm.org/get-certified). Survivors should be encouraged to use an ACSM-certified trainer when available.

Survivors at high risk for exercise-associated adverse events include those with a history of lung surgery or major abdominal surgery, an ostomy, cardiopulmonary comorbidities (eg, chronic obstructive pulmonary disease [COPD], chronic heart failure [CHF], CAD, cardiomyopathy), ataxia, severe nutritional deficiencies, extreme fatigue, or worsening/changing physical condition (ex, lymphedema exacerbation). These survivors should receive medical clearance and referral to trained personnel for a supervised exercise program.[506] In general, exercise should be individualized to the participant based on current exercise level and medical factors and should be progressed in terms of intensity, duration, and frequency as tolerated.

Survivors with lymphedema are considered at moderate risk if they are performing resistance/strength-training exercise of the affected limb, but are at low risk if they are participating in cardiovascular/aerobic exercise or strength training of unaffected limbs.[510-515] Resistance training in survivors with or at risk for lymphedema is discussed in more detail in *Resistance and Strength Training,* below.

Physical Activity Recommendations for Survivors

Both the American Cancer Society and the ACSM have made physical activity recommendations for cancer survivors.[483,484] The panel supports these recommendations and has adapted them as follows:

- All survivors should be encouraged to avoid inactivity or a sedentary lifestyle and return to daily activities as soon as possible.
- Survivors who are able should be encouraged to engage in daily physical activity, including exercise, routine activities, and recreational activities.
- Physical activity and exercise recommendations should be tailored to individual survivors' abilities and preferences.
- General recommendations for cancer survivors:
  - Overall volume of weekly activity should be at least 150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity, or an equivalent combination
  - Individuals should engage in 2 to 3 sessions per week of strength training (see *Resistance and Strength Training*, below) that include major muscle groups; and
  - Major muscle groups should be stretched on a routine basis.

The panel acknowledges that most survivors do not meet these exercise recommendations, and a significant portion report that they perform no leisure-time activity.[463,516] However, the evidence suggests that even light-intensity physical activity can improve physical functioning in survivors.[517] For survivors who are inactive, clinicians should not advise the immediate initiation of a high-intensity, high-frequency program.[518] Instead, the panel suggests that clinicians provide sufficient information to encourage survivors to avoid inactivity.[508] Survivors and providers should work together to develop incremental short- and long-term physical activity goals. These goals may include incremental increases in time spent in physical activity or in intensity of activity over time. The panel suggested a possible initial prescription (starting inactive survivors with 1 to 3 light-/moderate-intensity sessions of 20-minute or more per week, with progression based on tolerance) in the guidelines.[518] For survivors tolerating the minimum guideline recommendations, clinicians should consider encouraging variation within the exercise program or increasing the

amount of time engaged in physical activities/exercise modalities. Walking and using a stationary bike are safe for virtually all survivors.

Resistance and Strength Training

The health benefits of resistance training include improvement in muscle strength and endurance, improvements in functional status, and maintenance/improvement in bone density. Studies in survivors have shown improvements in lean body mass, muscular function, and upper body strength.[519-522] A recent systematic review of 15 studies of resistance training interventions during and/or after cancer treatment concluded that meaningful improvements in physiologic and quality-of-life outcomes can be achieved.[520] A similar review of 11 randomized controlled trials came to similar conclusions.[522] One recent study that included 2863 cancer survivors found resistance exercise to be associated with a 33% lower risk of all-cause mortality (95% CI, 0.45–0.99), independent of aerobic exercise.[523]

Multi-joint exercises (eg, chest press, shoulder press, squats, lunges, pushups) are recommended over exercises focused on a single joint, and all major muscle groups (chest, shoulders, arms, back, abdomen, and legs) should be incorporated into a resistance training program. For survivors who do not currently engage in resistance training, clinicians should recommend that they start with 1 set of each exercise and progress up to 2 to 3 sets as tolerated. A weight that would allow the performance of 10 to 15 repetitions is recommended; however, individualizing recommendations for resistance and strength training is important.

Strength training has been shown to be safe for survivors at risk for or with lymphedema and may even improve lymphedema symptoms.[510-514] Still, caution is advised in this population,[515] and referral to a lymphedema specialist for evaluation before starting a physical activity program that involves strength or resistance training of the affected limb should be considered. The panel lists special considerations for strength training in this population of survivors in the guidelines, including the use of compression garments, working with a professional trainer, slow progression as tolerated, and baseline and periodic evaluation of lymphedema. The National Lymphedema Network has published a position statement with additional guidance for exercise in individuals with lymphedema.[524]

Interventions to Increase Physical Activity

Dozens of studies have looked at the efficacy of a variety of behavioral and exercise interventions for increasing exercise behavior in cancer survivors.[484,525,526] However, data comparing different interventions are limited, and there is currently no “best” physical activity program for cancer survivors.[527-530] Several studies have examined the physical activity and counseling preferences of survivors, with the goal of informing possible strategies to best encourage increased activity in this population.[531-533]

The panel suggests several strategies to help increase physical activity. These strategies include a simple recommendation from a physician, physical therapist, and/or certified exercise physiologist.[534-536] In addition, participation in supervised exercise programs or classes or use of a pedometer may be helpful for survivors.[325,537-539] Print materials, telephone counseling, motivational counseling, and theory-based behavioral approaches (discussed in *Health Behavioral Change*, below) are other strategies that may be effective for increasing physical activity in the survivor population.[538-543]

Nutrition and Weight Management

Weight gain after cancer diagnosis and treatment is common.[544,545] The vast majority of studies on weight and weight gain in survivors have

been performed in survivors of breast cancer, but some studies have also been done in survivors of other cancers. Weight gain or being overweight or obese can exacerbate a survivor's risk for functional decline, comorbidity, and cancer recurrence or death, and can reduce quality of life.[544,546-553] For example, a systematic review and meta-analysis of studies in survivors of breast cancer found a correlation between higher body mass index (BMI) and higher risk of total and breast-cancer specific mortality.[548] Additionally, a recent meta-analysis demonstrated that this risk for increased breast cancer mortality is predominantly confined to the pre- and perimenopausal, ER+ population.[554] A retrospective study of survivors of stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that survivors with a BMI of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[471,474] In addition, some evidence suggests that weight loss or gain increases mortality risk in survivors, suggesting that weight maintenance is optimal.[555]

ASCO recently published a position statement on obesity and cancer.[556] The ASCO panel established an initiative to reduce the impact of obesity on cancer through education, tools, and resources for clinicians, by promoting research (ex, in health behavioral change), and by advocating for policies that can help patients with cancer manage their weight.

Nutrition and Weight Management Assessment

The BMI of survivors should be evaluated at regular intervals. A BMI of 18.5 to 24.9 kg/m^2 is considered ideal. It is important to inform patients of their weight status, particularly if they are underweight (BMI <18.5), overweight (BMI = 25–29.9), or obese (BMI ≥30), and discuss the importance of interventions to attain a normal body weight. The panel notes, however, that BMI should be considered in context of body composition. For more muscular survivors, waist circumference may be a better measure of overall disease risk. A waist circumference of >35 inches for women and >40 inches for men increases risk for diabetes, hypertension, and cardiovascular disease.[557]

Current dietary and physical activity habits and potential barriers to physical activity or a healthful diet of those in high-risk groups should be ascertained either by the oncologist or other appropriate allied health personnel (eg, nurses, dietitians). In addition, effects of cancer treatment and other medical issues should be assessed and addressed as necessary.

Weight Management for Survivors

Providers should discuss strategies to prevent weight gain for normal and overweight/obese survivors. Clinicians should reinforce the importance of maintaining a normal body weight throughout life and stress that weight management should be a priority for all cancer survivors. Regardless of BMI, all survivors should be advised about nutrition (see *Nutrition in Survivors*, below) and physical activity recommendations (see *Physical Activity*, above). For additional resources see the ASCO Tool Kit on Obesity and Cancer (http://www.asco.org/practice-research/obesity-and-cancer) and the LIVESTRONG MyPlate Calorie tracker (http://www.livestrong.com/myplate/).

Recommendations for Normal Weight Survivors

In addition to discussing nutrition (see *Nutrition in Survivors*, below) and physical activity (see *Physical Activity*, above), clinicians should reinforce the importance of maintaining a normal weight throughout life in survivors with a BMI in the normal range.

Recommendations for Overweight/Obese Survivors

Survivors with a BMI in the overweight or obese range should be engaged in discussions about nutrition, weight management, and physical activity, as outlined in these guidelines. In addition, clinicians should specifically discuss portion control and refer overweight/obese survivors to appropriate hospital-based or community resources. Referrals can also be made to a registered dietitian, especially those who are Certified Specialists in Oncology Nutrition (CSO) or members of the Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics. Diet, exercise, and behavioral modification are the cornerstones of weight management; however, in cases of morbid obesity pharmacologic agents or bariatric surgery can be considered with appropriate referral to primary care and other providers. Of note, the safety and efficacy of weight loss drugs or bariatric surgery in cancer survivors is currently unknown.

Recommendations for Underweight Survivors

Survivors with a BMI in the underweight range should be engaged in discussions about nutrition (see below). In addition, advising underweight survivors to increase their frequency of eating and to avoid fluid intake with meals may help with weight gain. Furthermore, smoking status, dental health, swallowing and taste/smell disorders, and gastrointestinal motility should be assessed and addressed as appropriate. Consideration can also be given to referral to a registered dietitian for individualized counseling.

Nutrition in Survivors

Systematic reviews and meta-analyses of observational studies have shown that healthy dietary patterns are associated with a decreased risk of primary cancer development.[558-561] A population study in England with >65,000 participants found that consumption of ≥7 servings daily of fruit and vegetables reduced cancer incidence by 25% (HR, 0.75; 95% CI, 0.59–0.96).[562]

Data also suggest that healthy dietary patterns (as characterized by plant-based diets that have ample amounts of fruits, vegetables, and whole grains, with limited quantities of red and processed meats and refined grains and sugars) are associated with a decrease in cancer recurrence and improved outcomes in survivors.[483,563] In survivors of stage III colon cancer, a diet consisting of more fruits, vegetables, whole grains, poultry, and fish, and less red meat, refined grains, and concentrated sweets was found to be associated with an improved outcome in terms of cancer recurrence and death, as well as overall survival.[564] Recent analysis of a stage III colon cancer adjuvant therapy trial found that higher dietary glycemic load (associated with high intakes of refined starches and sugars) was associated with an increased risk of recurrence and mortality in survivors.[565] The link between red and processed meats and mortality in survivors of non-metastatic colorectal cancer has been further supported by recent data from the Cancer Prevention Study II Nutrition Cohort, in which survivors with consistently high intakes of red and processed meat had a higher risk of colorectal cancer-specific mortality than those with low intakes (RR, 1.79; 95% CI, 1.11–2.89).[566] For survivors of non-colorectal cancers, the evidence linking a healthy diet with better outcomes is less robust. A study of 1901 survivors of early-stage breast cancer found that a diet higher in fruits, vegetables, whole grains, and poultry and lower in red and processed meats and refined grains resulted in a decreased risk of overall death and death from non-breast cancer causes, but was not associated with risk of breast cancer recurrence or death from breast cancer.[567]

All survivors should be encouraged to make informed choices about food to ensure variety and an adequate nutrient intake.

Recommendations for the composition of a healthy diet and food sources for those components are included in the guidelines. In general, a healthy diet is rich in plant sources, such as fruits, vegetables, whole grains, legumes, olive or canola oil, avocados, seeds, and nuts. Fish and poultry are recommended, while red and processed meats should be limited. Processed foods and foods and beverages with added sugars and/or fats should also be limited. In addition, survivors should be advised to limit alcohol intake to one drink per day for a woman and two drinks per day for a man.[483] Currently, no consensus regarding the role of soy foods in cancer control exists. Several large studies have found no adverse effects on breast cancer recurrence or total mortality related to the intake of soy food.[568-571] In fact, trends towards decreased recurrence and mortality were observed. The panel therefore considers moderate consumption of soy foods (≤3 servings a day) to be prudent.

The NCCN Survivorship Panel supports the following recommendations for a nutritious diet:

- Composition of diet
  - 2/3 (or more) vegetables, fruits, whole grains, or beans
  - 1/3 (or less) animal protein
- Sources of dietary components
  - Fat: plant sources such as olive or canola oil, avocados, seeds and nuts, and fatty fish
  - Carbohydrates: fruits, vegetables, whole grains, and legumes
  - Protein: poultry, fish, legumes, low-fat dairy foods, and nuts
- Limit intake of red or processed meat.

The use of healthy recipes, such as those found in resources such as the American Cancer Society's "Find Healthy Recipes" website: http://www.cancer.org/healthy/eathealthygetactive/eathealthy/findhealthyrecipes/index, should be encouraged.

Supplement Use in Survivors

Numerous systematic reviews and meta-analyses have assessed the role of various vitamins or other dietary supplements for the purposes of primary cancer prevention, cancer control, or preventing cancer recurrence.[572-584] No clear evidence supports an effect of dietary supplements for cancer prevention, control, or recurrence, although a few exceptions may warrant further studies.[585,586] Although the FDA regulates dietary supplement products under the Dietary Supplement Health and Education Act of 1994 (DSHEA),[587] analyses of dietary supplements from multiple manufacturers have found that many products do not contain the purported active ingredient and can contain unlisted ingredients such as cheap fillers (ex, rice, house plants) or banned pharmaceutical ingredients.[588,589] Furthermore, dietary supplements may remain available to consumers even following FDA class I drug recalls.[588]

Despite the lack of data supporting supplement use and the lack of assurance regarding supplement quality, as many as 81% of survivors take some vitamin or mineral dietary supplements, often without disclosing this information to their physicians.[590] Thus, the panel recommends that providers ask survivors about supplement use at regular intervals. The panel notes that supplement use is not recommended for most survivors, except in instances of documented deficiencies (eg, survivors of gastric cancer), inadequate diet, or comorbid indications (eg, osteoporosis,[591] ophthalmologic disorders,[592] cirrhosis[593,594]). Survivors should be advised that taking vitamin supplements does not replace the need for adhering to a healthy diet. If deemed necessary, referral to a registered dietitian, especially a CSO should be considered for guidance in supplement use.

Health Behavioral Change

Lifestyle behaviors are one area survivors can control if they are encouraged to change and are aware of resources to help them. Ambivalence about changing behavior is common in the general population, but among cancer survivors levels of motivation are often heightened, especially close to the time of diagnosis.[478,534,595]

Some data suggest that recommendations from the oncologist can carry significant weight for patients with cancer, yet many providers do not discuss healthy lifestyle changes with survivors.[534-536] Print materials and telephone counseling are other strategies that may be effective for improving healthy behavior in the survivor population, and several trials show support for these strategies.[538,539,542,543,596,597] In fact, a recent trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of colorectal cancer.[542,598] Moreover, results of the recently completed Reach Out to Enhance Wellness (RENEW) trial showed that an intervention of telephone counseling and mailed materials in 641 older, obese, and overweight survivors of breast, prostate, and colorectal cancers not only resulted in improved diet quality, weight loss, and physical activity but also had a long-lasting effect that was sustained a year after the intervention was complete.[538]

Another strategy, motivational counseling, may be an effective technique for increasing physical activity and other healthy behaviors in cancer survivors.[540,541] Motivational counseling focuses on exploring the survivor's thoughts, wants, and feelings and is directed at moving ambivalence so survivors choose to change their behavior.[599] Other behavioral strategies may also be useful, such as improving self-efficacy (ie, the belief that one can perform the actions of new activity and maintain this practice by addressing barriers and planning for behavior change) and self-monitoring.[600,601]

Continued on next page.

Immunizations and Prevention of Infections

Cancer survivors are at elevated risk for infection because of immune suppression associated with previous cancer treatments, such as chemotherapy, radiation, corticosteroids, certain surgeries, and stem cell transplantation. In fact, antibody titers to vaccine-preventable diseases decrease after anti-cancer treatment.[602,603] In addition, survivors are at increased risk of complications from vaccine-preventable diseases, such as those caused by human papillomaviruses (HPV) and influenza viruses.[603,604]

Many infections in survivors can be prevented by the use of vaccines. However, a recent report of data from the Behavioral Risk Factor Surveillance System (BRFSS) found that 42% of survivors did not receive an influenza vaccination in 2009, and 52% reported never receiving a pneumococcal vaccination.[463] Analysis of the SEER-Medicare database showed that survivors of breast cancer, aged 65 years or older, were less likely to receive an influenza vaccination than matched non-cancer controls.[88] A separate analysis of the SEER-Medicare database by another group found similar results.[605]

Vaccines represent a unique challenge in cancer and transplant survivors because they may not trigger the desired protective immune responses because of possible residual immune deficits.[606] In addition, certain vaccines, such as those that are live attenuated (eg, zoster; measles, mumps, rubella [MMR]), are contraindicated in actively immunosuppressed survivors because of an increased risk of developing the disease and/or prolonged shedding from the live organism given in the vaccine.

Risk Assessment and Screening for Immunizations and Prevention of Infections

Survivors are at elevated risk for infections if their cancer treatment included chemotherapy, monoclonal antibodies, radiation, corticosteroids, splenectomy, and/or hematopoietic cell transplantation (HCT; which includes peripheral blood stem cell transplantation, bone marrow transplantation, and cord blood transplantation). Risk is also elevated if the survivor has prior or current exposure to endemic infections or epidemics, or has a history of blood transfusion.

Interventions for Prevention of Infections

Infection in survivors can be prevented by education, antimicrobial prophylaxis, and the judicious use of vaccines.

Antimicrobial Prophylaxis and Education

Survivors should be educated about safe pet care/the avoidance of zoonosis, travel precautions, and gardening precautions.[607-612] Safe pet care tips include washing hands with soap and running water after handling animals and their feces. If possible, survivors should avoid direct contact with animal feces. Travel precautions include education on the need for pre-travel vaccines, prophylaxis against specific infections, and education on how to prevent waterborne, airborne, and zoonotic infections. Travelers may find useful information at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-8-advising-travelers-with-specific-needs/immunocompromised-travelers or through consulting a travel clinic. Gardening precautions include wearing gloves to avoid cuts and punctures that could be delayed in healing or become infected with fungus or staphylococcus/streptococcus that may be present on thorns, and wearing a protective mask to avoid inhalation of spores.

For information regarding antimicrobial prophylaxis, please see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (available online at www.NCCN.org).

Immunizations

Vaccination, or "active immunization" involves administration of all or part of a microorganism or a modified product of a microorganism (eg, a toxoid, a purified antigen, or an antigen produced by genetic engineering) to produce an immunologic response that mimics that of natural infection but usually presents little or no risk to the recipient. The use of vaccines that do not contain live organisms should be considered and encouraged in all cancer and transplant survivors who have completed therapy at least 3 months before the planned vaccine administration. In general, the usual doses and schedules are recommended, as outlined by the Advisory Committee on Immunization Practices (ACIP).[613,614] The Infectious Diseases Society of America (IDSA) has outlined guidance for vaccination in immunocompromised patients, including those with cancer and those post-HCT.[615] The NCCN Survivorship Panel outlined immunization guidelines specific to survivors of hematologic malignancies and solid tumors, with separate guidelines for survivors who received HCT. In survivors who received anti–B-cell antibody therapy, vaccination should be delayed for at least 6 months after chemotherapy or the last dose of such therapy to allow for reconstitution of the B-cell population. More details are available in the guidelines.

Before vaccination, immune system viability and history of allergic reactions to vaccines should be assessed. Baseline WBC counts should be in the normal range or within reasonable limits before starting vaccinations, unless they are elevated because of disease status. The survivor should not be on immunosuppressive drugs or chemotherapy, and ongoing infection should not be present.

The following vaccines should be considered and encouraged for all survivors, administered according to the usual doses and schedules: influenza vaccine (only inactivated or recombinant); pneumococcal vaccine (PPSV-23/PCV-13); tetanus, diphtheria, pertussis (Tdap); and HPV (in survivors aged ≤26 years old or younger).[616-618] These vaccines do not contain live organisms; instead they contain inactivated organisms, purified antigens, bacterial components, or genetically engineered recombinant antigens. The effectiveness of these vaccinations might be suboptimal because of lingering immune suppression.[606] However, in the absence of known harm, their administration may be worthwhile with the hope of achieving some protection.

Other vaccines, as listed in the guidelines, should be considered in consultation with an infectious disease or travel medicine specialist if unique circumstances in the survivor's lifestyle, upcoming travel, or local epidemic/risks merit their use.

Influenza Vaccines

Annual influenza vaccination is recommended for all cancer and transplant survivors. Live attenuated influenza vaccines should generally be avoided in this population. Preferred vaccines include inactivated influenza vaccines (ie, trivalent [IIV3] standard-dose, trivalent [IIV3] high-dose, and quadrivalent [IIV4] standard-dose) or, for individuals with egg allergies, recombinant influenza vaccine (ie, trivalent [RIV3]).[614,619] To date, no evidence shows superiority of any one of these vaccines.

Live Viral Vaccines

Vaccines that contain live attenuated organisms (eg, live-attenuated influenza vaccine; MMR; oral polio vaccine [OPV]) are contraindicated in actively immunocompromised survivors because of a proven or

theoretical increased risk of disease and prolonged shedding from the live organism present in the vaccine. They should not be offered to actively immunocompromised survivors, unless cleared by a clinician experienced in vaccine use or by an infectious disease specialist. However, live viral vaccines can be administered to immunocompetent survivors 3 or more months after treatment, but consultation with an infectious disease specialist or clinician familiar with vaccination in patients with cancer is recommended. An exception is the live-attenuated influenza vaccine, which should be avoided in survivors because safer alternatives exist (see earlier discussion).

Healthy immunocompetent individuals who live in a household with immunocompromised survivors can receive the following live vaccines: MMR, rotavirus vaccine in infants aged 2 to 7 months, varicella vaccine (VAR), and zoster vaccine. However, OPV should not be administered to individuals who live in a household with immunocompromised survivors. Highly immunocompromised survivors should avoid handling diapers of infants who have received the rotavirus vaccine for 4 weeks after vaccination. Immunocompromised survivors should avoid contact with persons who develop skin lesions after receipt of VAR or zoster vaccine until the lesions clear.

Zoster (Shingles) Vaccine

A single dose of zoster (shingles) vaccine is recommended for survivors aged 60 years or older without active or ongoing immunodeficiency, no history of cellular immunodeficiency or HCT, and who have not received chemotherapy or radiation within the past 3 months, or it can be given at least 4 weeks before initiation of chemotherapy or immunosuppressive drugs.[615,620,621] Zoster vaccination should also be considered for survivors aged 50 to 59 years with a history of varicella or zoster infection (VZV) or VZV seropositivity with no previous doses of varicella vaccine. The zoster vaccine should be avoided in immunocompromised survivors, but can be considered in transplant survivors without active graft-versus-host disease (GVHD) or enhanced immunosuppression 24 or more months after transplantation.

Continued on next page.

Summary

With improved diagnostic and treatment modalities, the population of cancer survivors is rapidly growing. Many survivors will experience late and/or long-term effects of cancer and its treatment that can include physical and/or psychosocial problems. These issues need to be addressed in a regular and systematic manner. Unfortunately, many of these effects are not addressed until discharge from the oncologist and interventions may be left to health care providers who may not have much experience treating the concerns of cancer survivors. The NCCN Survivorship Panel hopes that these guidelines can help both oncologic and primary health care professionals lessen the burden left on survivors by their cancer experience so they can transition back to a rewarding life.

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