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Survivorship, Version 2.2018:

Clinical Practice Guidelines in Oncology

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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 ma-jor NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Survivorship are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Survivorship Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.
Individual disclosures for the NCCN Survivorship Panel members can be found on page 1247. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)
These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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Abstract

The NCCN Guidelines for Survivorship provide screening, evaluation, and treatment recommendations for common physical and psychosocial consequences of cancer and cancer treatment to help healthcare professionals who work with survivors of adult-onset cancer in the posttreatment period. This portion of the guidelines describes recommendations regarding the management of anthracycline-induced cardiotoxicity and lymphedema. In addition, recommendations regarding immunizations and the prevention of infections in cancer survivors are included.

Anthracycline-Induced Cardiac Toxicity

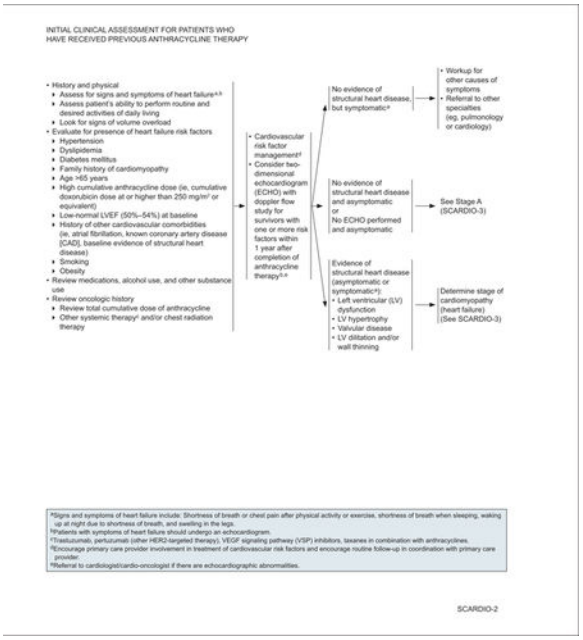
Many cancer treatments, including chemotherapeutics, targeted agents, hormonal therapies, and radiation, are associated with cardiovascular toxicities.[1–7] Cardiovascular sequelae can include arrhythmias, pericardial disease, hypertension, thrombosis, cardiomyopathy/heart failure, and vascular and metabolic issues. Survivors of some cancer types have a markedly increased risk of developing cardiovascular disease compared with noncancer populations.[8]

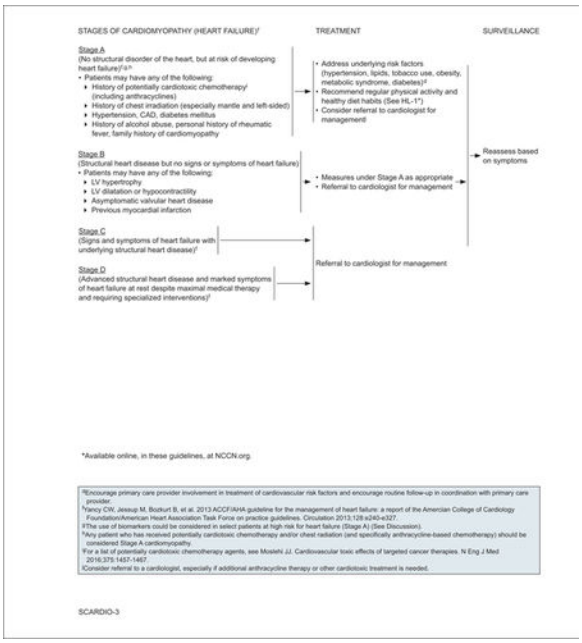
As a result, a new field called “cardiooncology,” focused on the cardiovascular health of patients with cancer and survivors, has become established.[9,10]

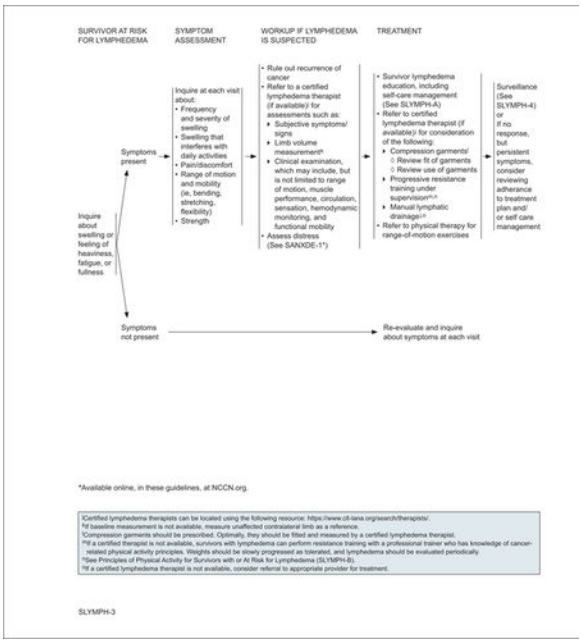
Anthracyclines (eg, doxorubicin, epirubicin, daunorubicin) are used to treat many cancer types, including lymphoma, sarcoma, and breast cancer, and are among the best studied and most common causes of cancer treatment-induced cardiac injury.[11–13] The mechanism by which anthracyclines cause cardiomyopathy is not fully understood, but likely involves the formation of reactive oxygen species, oxidative injury, and the subsequent induction of apoptosis in cardiac cells.[14] A role for topoisomerase-IIβ in cardiomyocytes in the production of reactive oxygen species in response to anthracyclines has been suggested.[15]

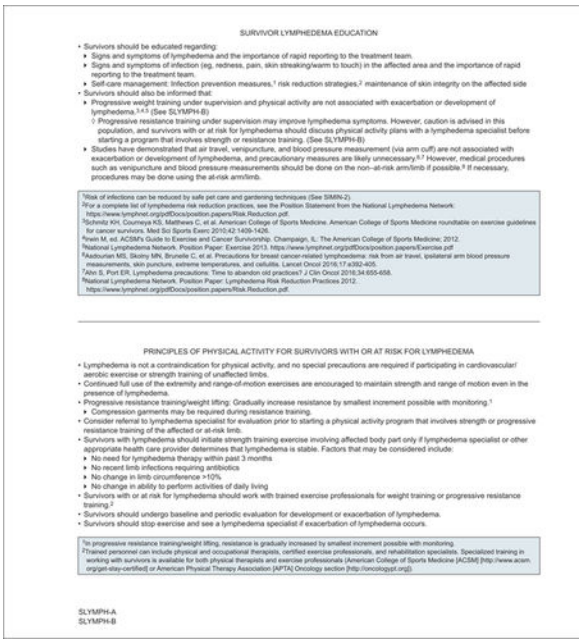
Studies suggest that the incidence of clinical congestive heart failure after anthracycline-based therapy for adult-onset cancer is <5%.[16–19] For instance, in the NSABP B-31 trial of patients with breast cancer, the rates of symptomatic heart failure after 7 years were 4% in patients treated with anthracycline-based chemotherapy and trastuzumab and 1.3% in those treated with anthracycline-based chemotherapy alone.[18] However, a significantly higher percentage of patients have evidence of subclinical heart failure, with reports of asymptomatic left ventricular ejection fraction (LVEF) decline being 9% to 50% in various studies.[16,20–22]

The panel has focused specifically on anthracycline-induced cardiac toxicity in these guidelines. Other systemic therapies (eg, HER2-targeted agents, angiogenesis inhibitors, immunotherapies) may cause cardiomyopathy or other myopathies like myocarditis,[2,23,24] 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 those induced by anthracyclines.[2] 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, which could occur, for example, as a result of radiation therapy.[25]









SURVIVOR LYMPHEDEMA EDUCATION

- Survivors should be educated regarding:
  - Signs and symptoms of lymphedema and the importance of rapid reporting to the treatment team.
  - Signs and symptoms of infection (eg, redness, pain, skin streaking/warm to touch) in the affected area and the importance of rapid reporting to the treatment team.
  - Self-care management: Infection prevention measures,[1] risk reduction strategies,[2] maintenance of skin integrity on the affected side
- Survivors should also be informed that:
  - Progressive weight training under supervision and physical activity are not associated with exacerbation or development of lymphedema.[3,4,5] (See SLYMPH-B)
    - Progressive resistance training under supervision may improve lymphedema symptoms. However, caution is advised in this population, and survivors with or at risk for lymphedema should discuss physical activity plans with a lymphedema specialist before starting a program that involves strength or resistance training. (See SLYMPH-B)
  - Studies have demonstrated that air travel, venipuncture, and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary.[6,7] However, medical procedures such as venipuncture and blood pressure measurements should be done on the non–at-risk arm/limb if possible.[8] If necessary, procedures may be done using the at-risk arm/limb.

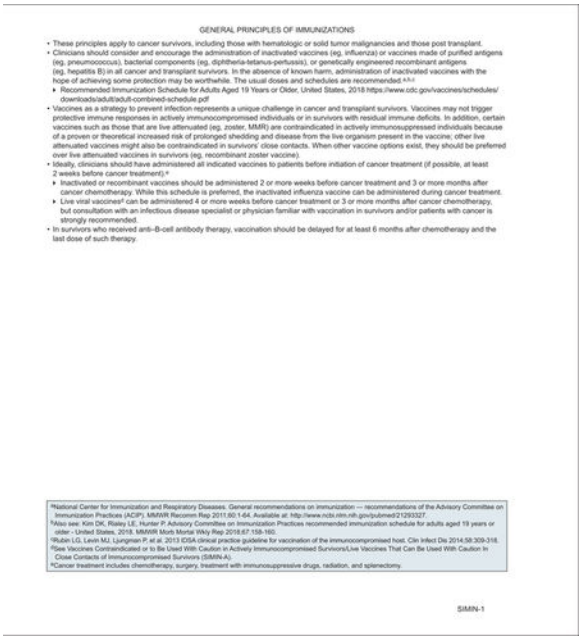
[1]Risk of infections can be reduced by safe pet care and gardening techniques (See SIMIN-2).
[2]For a complete list of lymphedema risk reduction practices, see the Position Statement from the National Lymphedema Network: https://www.lymphnet.org/pdfDocs/position.papers/Risk.Reduction.pdf.
[3]Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409-1426.
[4]Irwin M, ed. ACSM's Guide to Exercise and Cancer Survivorship. Champaign, IL: The American College of Sports Medicine; 2012.
[5]National Lymphedema Network. Position Paper: Exercise 2013. https://www.lymphnet.org/pdfDocs/position.papers/Exercise.pdf
[6]Asdourian MS, Skolny MN, Brunelle C, et al. Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis. Lancet Oncol 2016;17:e392-405.
[7]Alvi S, Port ER. Lymphedema precautions: Time to abandon old practices? J Clin Oncol 2016;34:655-658.
[8]National Lymphedema Network. Position Paper: Lymphedema Risk Reduction Practices 2012. https://www.lymphnet.org/pdfDocs/position.papers/Risk.Reduction.pdf.

PRINCIPLES OF PHYSICAL ACTIVITY FOR SURVIVORS WITH OR AT RISK FOR LYMPHEDEMA

- Lymphedema is not a contraindication for physical activity, and no special precautions are required if participating in cardiovascular/aerobic exercise or strength training of unaffected limbs.
- 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.
- Progressive resistance training/weight lifting: Gradually increase resistance by smallest increment possible with monitoring.[1]
  - Compression garments may be required during resistance training.
- Consider referral to lymphedema specialist for evaluation prior to starting a physical activity program that involves strength or progressive resistance training of the affected or at-risk limb.
- Survivors with lymphedema should initiate strength training exercise involving affected body part only if lymphedema specialist or other appropriate health care provider determines that lymphedema is stable. Factors that may be considered include:
  - 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
- Survivors with or at risk for lymphedema should work with trained exercise professionals for weight training or progressive resistance training.[2]
- Survivors should undergo baseline and periodic evaluation for development or exacerbation of lymphedema.
- Survivors should stop exercise and see a lymphedema specialist if exacerbation of lymphedema occurs.

[1]In progressive resistance training/weight lifting, resistance is gradually increased by smallest increment possible with monitoring.
[2]Trained personnel can include physical and occupational therapists, certified exercise professionals, and rehabilitation specialists. Specialized training in working with survivors is available for both physical therapists and exercise professionals (American College of Sports Medicine [ACSM] [http://www.acsm.org/get-stay-certified] or American Physical Therapy Association [APTA] Oncology section [http://oncologypt.org]).

SLYMPH-A
SLYMPH-B

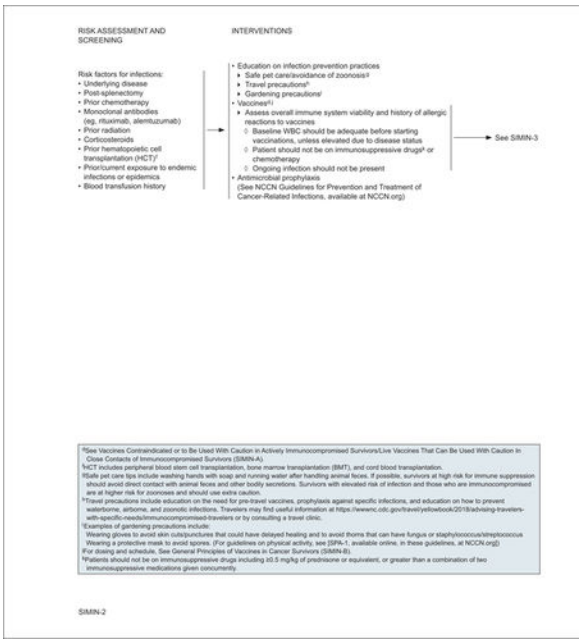


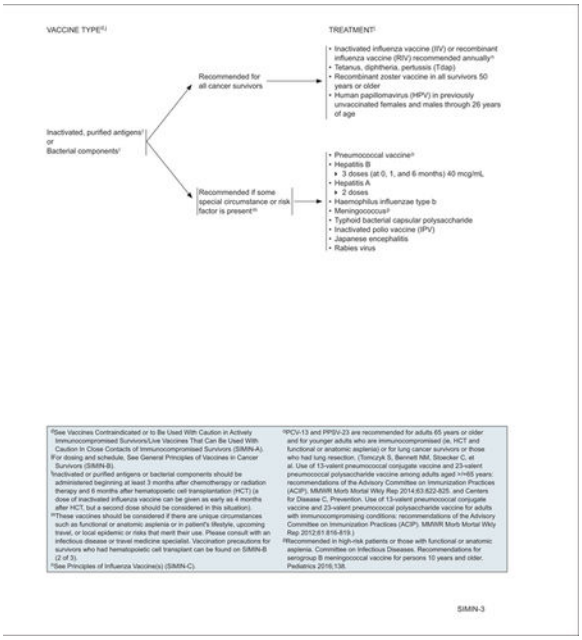
GENERAL PRINCIPLES OF IMMUNIZATIONS

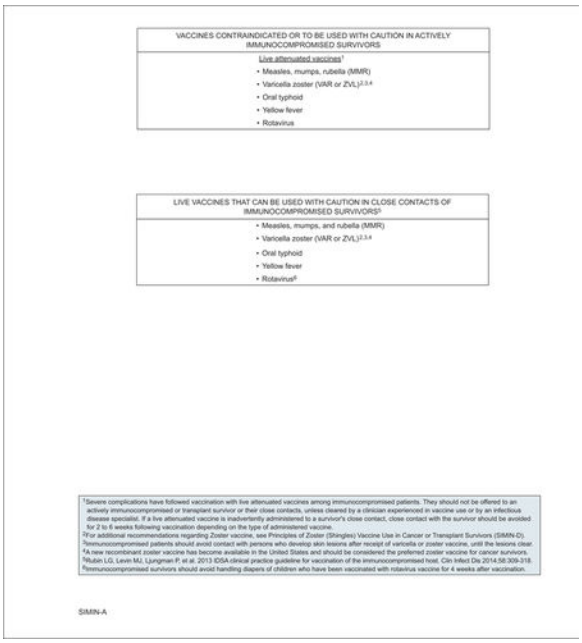
- These principles apply to cancer survivors, including those with hematologic or solid tumor malignancies and those post transplant.
- Clinicians should consider and encourage the administration of inactivated vaccines (eg, influenza) or vaccines made of purified antigens (eg, pneumococcus), bacterial 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]
  - Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2018:https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf
- 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. When other vaccine options exist, they should be preferred over live attenuated vaccines in survivors (eg, recombinant zoster vaccine).
- Ideally, clinicians should have administered all indicated vaccines to patients before initiation of cancer treatment (if possible, at least 2 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[e] 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 strongly 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]National Center for Immunization and Respiratory Diseases. 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]Also see: Kim DK, Riley LE, Hunter P. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2018. MMWR Morb Mortal Wkly Rep 2018;67:158-160.
[c]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.
[d]See Vaccines Contraindicated or to Be Used With Caution in Actively Immunocompromised Survivors/Live Vaccines That Can Be Used With Caution In Close Contacts of Immunocompromised Survivors (SIMIN-A).
[e]Cancer treatment includes chemotherapy, surgery, treatment with immunosuppressive drugs, radiation, and splenectomy.

SIMIN-1







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

Live attenuated vaccines[1]

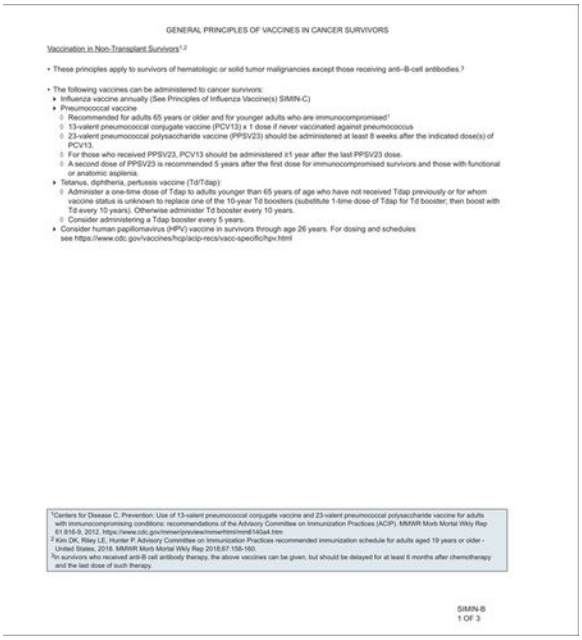
- Measles, mumps, rubella (MMR)
- Varicella zoster (VAR or ZVL)[2,3,4]
- Oral typhoid
- Yellow fever
- Rotavirus

LIVE VACCINES THAT CAN BE USED WITH CAUTION IN CLOSE CONTACTS OF IMMUNOCOMPROMISED SURVIVORS[5]

- Measles, mumps, and rubella (MMR)
- Varicella zoster (VAR or ZVL)[2,3,4]
- Oral typhoid
- Yellow fever
- Rotavirus[6]

[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]Immunocompromised patients should avoid contact with persons who develop skin lesions after receipt of varicella or zoster vaccine, until the lesions clear.
[4]A new recombinant zoster vaccine has become available in the United States and should be considered the preferred zoster vaccine for cancer survivors.
[5]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.
[6]Immunocompromised survivors should avoid handling diapers of children who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination.

SIMIN-A



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
    - Recommended for adults 65 years or older and for younger adults who are immunocompromised[1]
    - 13-valent pneumococcal conjugate vaccine (PCV13) x 1 dose if never vaccinated against pneumococcus
    - 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be administered at least 8 weeks after the indicated dose(s) of PCV13.
    - For those who received PPSV23, PCV13 should be administered ≥1 year after the last PPSV23 dose.
    - A second dose of PPSV23 is recommended 5 years after the first dose for immunocompromised survivors and those with functional or anatomic asplenia.
  - Tetanus, diphtheria, pertussis vaccine (Td/Tdap):
    - Administer a one-time dose of Tdap to adults younger than 65 years of age 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 administer Td booster every 10 years.
    - Consider administering a Tdap booster every 5 years.
  - Consider human papillomavirus (HPV) vaccine in survivors through age 26 years. For dosing and schedules see https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html

[1]Centers for Disease C, Prevention. 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 61:816-9, 2012. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm
[2]Kim DK, Riley LE, Hunter P. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2018. MMWR Morb Mortal Wkly Rep 2018;67:158-160.
[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.

SIMIN-B
1 OF 3

GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

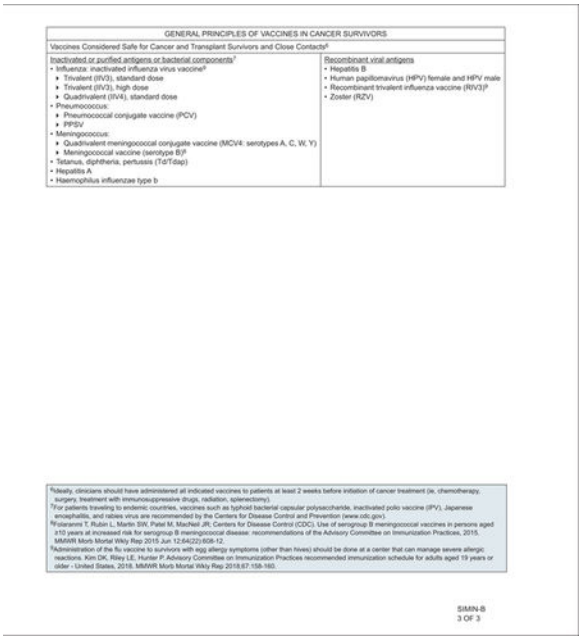
Vaccination in Hematopoietic Cell Transplant (HCT) Survivors[a,b]

- 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 Tdap should be considered (can replace second and third dose by Td).
- Hepatitis B (HepB) 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 survivors through age 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
    - MMR vaccine should be avoided within 4 weeks before HCT.
    - 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.

Continued

[a]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318. http://www.ncbi.nlm.nih.gov/pubmed/24421306.
[b]HCT includes peripheral blood stem cell transplantation, bone marrow transplantation (BMT), and cord blood transplantation.

SIMIN-B
2 OF 3



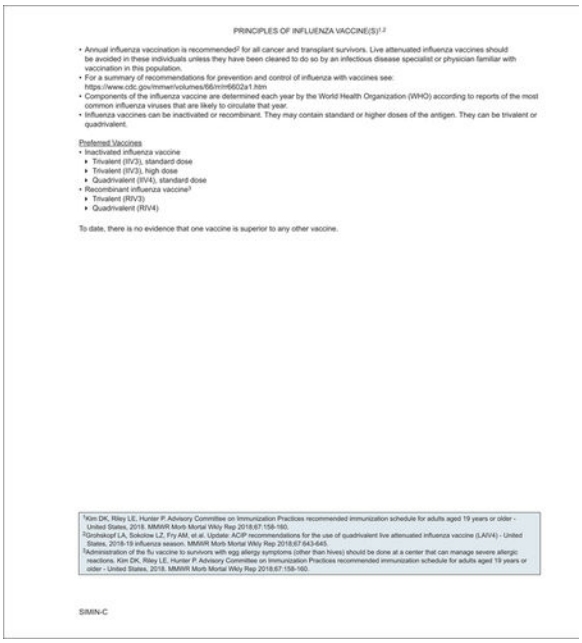
GENERAL PRINCIPLES OF VACCINES IN CANCER SURVIVORS

Vaccines Considered Safe for Cancer and Transplant Survivors and Close Contacts[a]

Inactivated or purified antigens or bacterial components[f]	Recombinant viral antigens
• Influenza: inactivated influenza virus vaccine[g] ▸ Trivalent (IIV3), standard dose ▸ Trivalent (IIV3), high dose ▸ Quadrivalent (IIV4), standard dose • Pneumococcus: ▸ Pneumococcal conjugate vaccine (PCV) ▸ PPSV • Meningococcus: ▸ Quadrivalent meningococcal conjugate vaccine (MCV4: serotypes A, C, W, Y) ▸ Meningococcal vaccine (serotype B)[j] • Tetanus, diphtheria, pertussis (Td/Tdap) • Hepatitis A • Haemophilus influenzae type b	• Hepatitis B • Human papillomavirus (HPV) female and HPV male • Recombinant trivalent influenza vaccine (RIV3)[k] • Zoster (RZV)

[a]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).
[f]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).
[g]Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2008 Jan 25;57(RR-5):1-30.
[j]Bilukha O, Rosenstein N; Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease--recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2005 Aug 26;54(RR-7):1-21.
[k]Grohskopf LA, Sokolow LZ, Broder KR, Olsen SJ, Karron RA, Jernigan DB, Bresee JS; Advisory Committee on Immunization Practices - United States, 2017-18 Influenza Season. MMWR Morb Mortal Wkly Rep 2017 Aug 4;66(2):1-20.

SIMIN-B
3 OF 3



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

- Annual influenza vaccination is recommended[2] 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: https://www.cdc.gov/mmwr/volumes/66/rr/rr6602a1.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 or recombinant. They may contain standard or higher doses of the antigen. They can be trivalent or quadrivalent.

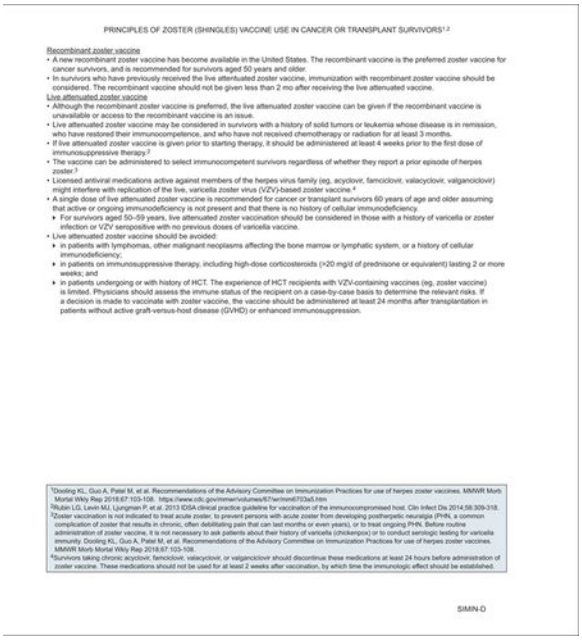
Preferred Vaccines

- Inactivated influenza vaccine
  - Trivalent (IIV3), standard dose
  - Trivalent (IIV3), high dose
  - Quadrivalent (IIV4), standard dose
- Recombinant influenza vaccine[3]
  - Trivalent (RIV3)
  - Quadrivalent (RIV4)

To date, there is no evidence that one vaccine is superior to any other vaccine.

[1]Kim DK, Riley LE, Hunter P. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2018. MMWR Morb Mortal Wkly Rep 2018;67:158-160.
[2]Grohskopf LA, Sokolow LZ, Fry AM, et al. Update: ACIP recommendations for the use of quadrivalent live attenuated influenza vaccine (LAIV4) - United States, 2018-19 influenza season. MMWR Morb Mortal Wkly Rep 2018;67:643-645.
[3]Administration of the flu vaccine to survivors with egg allergy symptoms (other than hives) should be done at a center that can manage severe allergic reactions. Kim DK, Riley LE, Hunter P. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2018. MMWR Morb Mortal Wkly Rep 2018;67:158-160.

SIMIN-C



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

Recombinant zoster vaccine

- A new recombinant zoster vaccine has become available in the United States. The recombinant vaccine is the preferred zoster vaccine for cancer survivors, and is recommended for survivors aged 50 years and older.
- In survivors who have previously received the live attenuated zoster vaccine, immunization with recombinant zoster vaccine should be considered. The recombinant vaccine should not be given less than 2 mo after receiving the live attenuated vaccine.

Live attenuated zoster vaccine

- Although the recombinant zoster vaccine is preferred, the live attenuated zoster vaccine can be given if the recombinant vaccine is unavailable or access to the recombinant vaccine is an issue.
- Live attenuated 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 live attenuated zoster vaccine is given prior to starting therapy, it should be administered at least 4 weeks prior to the first dose of immunosuppressive therapy.[3]
- 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 live attenuated 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 aged 50–59 years, live attenuated 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.
- Live attenuated zoster vaccine should be avoided:
  - in patients with lymphomas, other malignant neoplasms affecting the bone marrow or lymphatic system, or a history of cellular immunodeficiency;
  - in patients on immunosuppressive therapy, including high-dose corticosteroids (>20 mg/d of prednisone or equivalent) lasting 2 or more weeks; and
  - 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]Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep 2018;67:103-108. https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a5.htm
[2]Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.
[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. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep 2018;67:103-108.
[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.

SIMIN-D

Panel Considerations Regarding Anthracycline-Induced Cardiac Toxicity

Anthracycline-induced heart failure may take years or decades 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, before the development of symptoms.[26] Additionally, data from these other types of cardiac injury suggest that early intervention with cardioprotective medications results in better long-term cardiac function.[27,28] It is possible that if anthracycline-induced cardiac dysfunction is detected early, it may

also be responsive to cardioprotective medications.[2,26–29] In fact, data from a prospective study that followed 2,625 patients who received anthracycline-containing therapy through the survivorship phase suggest that early initiation of heart failure therapy may allow for at least partial recovery of LVEF in this population.[20] In this study, survivors were started on treatment when LVEF decreased by >10 absolute points and was <50%. A full recovery was observed in 11% of treated survivors (LVEF increased to the baseline value), and 71% had partial recovery (LVEF increased by >5 absolute points and reached >50%). In addition, a growing body of preclinical, observational, and pilot research suggests that lifestyle changes, such as weight control,[30–32] dietary modification (either through correcting dietary deficiencies or increasing intakes of various nutrients),[33] and exercise,[34–38] may also be helpful at these early stages, before the onset of heart failure symptoms, although more research is necessary.[39,40]

These emerging issues in anthracycline-induced cardiomyopathy are consistent with the changes in the cardiology community's approach to 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.[41] In 2001, the AHA/ACC guidelines proposed a new classification for heart failure.41 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 Guide-lines 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 (ie, 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 subsequently. The panel also believes that early involvement of a cardio-oncologist or cardiologist in the care of the cancer survivor is important. Therefore, 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.[42]

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).[41] This revised classification has both diagnostic and therapeutic utility, because evidence suggests that treatments prescribed in the absence of structural heart abnormalities or symptoms can reduce the morbidity and mortality of heart failure in the general population.[2,20,26–29] Left untreated, however, the accumulation of cardiac risk factors 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 (NYHA) functional classification of heart failure.[43] In this system, which is based on limitations to physical activity and the effect of physical activity on heart failure symptoms, NYHA class I is similar to AHA/ACC stage B, while NYHA class II and III would be considered AHA/ACC stage C and NYHA class 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.[44] The review also found no direct evidence showing the effectiveness of cardiac treatment on outcomes of asymptomatic survivors.[44] 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.[45] Some reasons for the lack of data on screening survivors for cardiotoxicity have been discussed,[46] and, unfortunately, high-quality data have not been forthcoming since ASCO's 2007 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 comparable imaging to evaluate cardiac anatomy and function 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). An international collaborative supports lifelong echocardiographic surveillance at least every 5 years in survivors of childhood cancer treated with anthracyclines.[47] Although the frequency of cardiac assessment using echocardiograms or multigated acquisition (MUGA) scans in this population has been a matter of debate, there is general support for at least one assessment in children who have completed anthracycline therapy.[48,49]

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.[50] 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.

In 2017, ASCO released a clinical practice guideline for the prevention and monitoring of cardiac dysfunction in survivors of adult cancers.[51] The ASCO panel gave a moderate-strength recommendation (as based on evidence and the balance between harms and benefits) that echocardiogram can be performed for asymptomatic survivors deemed to be at increased risk for cardiac dysfunction at 6 to 12 months after treatment, including survivors with a history of anthracycline therapy. Insufficient evidence prevented the ASCO panel from making a recommendation regarding the frequency and duration of additional surveillance of survivors who are asymptomatic and who showed no signs of cardiac dysfunction on initial assessment.

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 subsequently).

Assessment for Symptoms of Heart Failure:

According to the 2013 AHA/ACC guidelines, 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).[52] 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.[1,7,9,53] 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.[54] Older survivors, those with a higher cumulative anthracycline dose (cumulative doxorubicin dose of 250 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. Recent data also showed that being overweight or obese is a risk factor for cardiotoxicity from anthracyclines in breast cancer survivors.[55] In addition, the risk of cardiac events and death in survivors of breast cancer has been shown to increase as the number of cardiovascular risk factors increases.[56]

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 after anthracycline therapy associated with an increased risk for the future development of symptomatic heart failure? 3) Does the recognition of cardiac abnormalities and treatment of cardiac risk factors after anthracycline therapy affect outcomes?

As for the prevalence of structural heart disease in patients treated with anthracyclines, a study of 2,625 patients with cancer (mostly breast cancer or non-Hodgkin's lymphoma) assessed LVEF before, every 3 months during anthracycline chemotherapy and during the following year, every 6 months for the next 4 years, and annually after that.[20] Cardiotoxicity, defined as LVEF <50% and decreased by >10 absolute points, was observed in 9% of the study population. 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.[57] More than 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 nonclinical trial population of patients with cancer, many may already have cardiac risk factors or actual cardiomyopathy before 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.

Regarding the second question, little is known regarding the natural history of heart failure in survivors with stage B heart failure after anthracycline therapy, and the long-term prognosis of survivors with cardiac structural abnormalities after anthracycline exposure is not known. However, regarding the final question, 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 with place-bo (P=.03).[29] 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 re-ceiving 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.[28] 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.[26] In addition, in the larger study by this group (2,625 patients), heart failure therapy was initiated in all patients with LVEF <50% that had decreased by >10 absolute points, and 82% of patients experienced a full or partial recovery.[20] In the noncancer setting, a randomized controlled trial of >4,200 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).[27]

Considering these data, the panel believes that survivors with one or more risk factors who have completed anthracycline therapy can be considered for assessment for structural heart disease with ap-propriate cardiac imaging within 12 months of the last anthracycline dose. In one study with a median follow-up of 5.2 years, 98% of cases of cardiotoxicity were observed within the first year after treatment.[20] The prevalence of late-onset cardiotoxicity has not been well studied beyond 5 years. Risk fac-tors to consider include age >65 years, a high cumulative anthracycline dose, underlying cardiovascular disease/risk factors, or a low-normal baseline LVEF.[13]

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.[58,59] It can recognize early stages of heart failure by revealing abnormalities of the pericardium, myocardium, and heart valves.[52] Although 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.[58,60]

In agreement with these guidelines, ASCO's guidelines that address monitoring of cardiac toxicity after treatment in survivors of adult-onset cancer indicate that echocardiogram can be considered for asymptomatic survivors deemed to be at increased risk for cardiac dysfunction, including survivors with a history of anthracycline therapy.[51]

Biomarkers:

The panel recognizes the growing body of literature suggesting the possible utility of cardiac biomarkers (specifically troponin) as a noninvasive marker of cardiotoxicity. The panel believes that more prospective, multi-institutional studies are needed, but that biomarker use can be considered in select patients at high risk for heart failure. 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.[61] A systematic re-view of the role of posttreatment cardiac troponins as predictive markers of anthracycline-induced left ventricular dysfunction revealed few studies and in-consistent data.[62] The utility of other potential cardiac biomarkers have been reviewed elsewhere.[60]

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 cardiovas-cular 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.[63] 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 subsequently.

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, coronary artery disease, diabetes mellitus, a family history of heart failure, or a history of cardiotoxins such as anthracyclines. Therefore, all survivors with exposure to anthracyclines have, by definition, at least one risk factor that pre-disposes them to cardiac disease and should be treated as appropriate. Other anti-cancer systemic therapies are potentially cardiotoxic and may increase the risk of cardiac disease.[4] Involvement of the survivor’s primary care provider in the management of survivors with cardiac risk factors is encouraged. Management can include addressing underlying risk factors, recommending physical activity and healthy dietary habits, and referral to a cardiologist.

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.[26]

Lymphedema

Lymphedema is a common side effect of cancer treatment, occurring on the same side of the body as the cancer treatment, resulting from damage to the lymphatic system. It occurs when lymph fluid accumulates in the interstitial tissue, causing swelling of the limb or other areas such as the neck, trunk, or genitals. Lymphedema is most often diagnosed within 18 months of treatment; however, it can develop any time in the life of the survivor.

More than 20% of cancer survivors reported lymphedema as a physical concern in a survey of almost 14 million survivors in the United States in a 2010 LIVESTRONG study.[64] The incidence of lymphedema varies by disease site. In one study, 41% of almost 1,000 breast cancer survivors developed lymphedema by 10-year follow-up.[65] In a study of survivors of gynecologic cancers, the incidence of lymphedema 2 years after surgery was 37%.[66] In one study of 431 survivors of melanoma who had been treated with complete lymph node dissection and/or wide local excision and axillary or inguinal sentinel lymph node surgery, the reported incidence of lymphedema was 25%.[67]

Lymphedema may cause or exacerbate psychological distress.[68,69] In a study that included 692 breast cancer survivors with lymphedema, almost half reported moderate to extreme distress related to their lymphedema.[70] Lymphedema can also affect social roles, employment, physical function, and quality of life and can cause disability.[71–73] Unfortunately, only 55% of cancer survivors with self-reported lymphedema in the LIVESTRONG study said that they received care for lymphedema.[64]

Risk Factors for Lymphedema

Survivors whose cancer treatment included surgery and/or radiation to the axillary, supraclavicular, cervical, or inguinal lymph node system are at risk for the development of lymphedema.[74–77] Sentinel lymph node biopsy also appears to increase the risk of lymphedema, although it poses less risk than complete dissection or radiation to the nodal group, and data are not completely consistent.[75,78–82] Other treatment-related factors that have been associated with an increased risk of lymphedema are receipt of chemotherapy or radiation and the extent of lymph node dissection.[65,66,74–77,80,82–84] Overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2), localized infection, and higher initial stage of disease also raise the risk of lymphedema development.[65,66,74,75,77,82,84–86]

Assessment and Workup for Lymphedema

Survivors with a history of radiation or surgery to the lymph nodes should be asked about swelling or feeling of heaviness, fatigue, or fullness at each visit. Early detection and diagnosis is key for optimal lymphedema management, because stages 0 and 1 are reversible, whereas stages 2 and 3 are less responsive to treatment (see “Definition and

Stages of Lymphedema," page 1221)). Swelling on the same side as the cancer treatment is a universal symptom of lymphedema. Additional initial symptoms may include pain or discomfort and/or sensations of heaviness, fatigue, fullness, and/or tightness in the skin. Symptoms, including decreased range of motion or strength and thickening of the skin, may occur in later stages. If symptoms are present, survivors should be asked about the frequency and severity of swelling, pain and/or discomfort, any issues with strength or range of motion and mobility (ie, bending, stretching, flexibility), and whether symptoms interfere with daily activities.

If lymphedema symptoms are present, a recurrence of cancer should be ruled out. The survivor should then be referred to a certified lymphedema therapist, if available, for additional assessments. These assessments can include subjective signs and symptoms of lymphedema and limb volume measurements. Ideally, pretreatment limb measurement of both sides should be performed as a baseline before initiation of any therapy for those with treatment-related or individual risk factors. If not, the contralateral limb can be used for comparison in the posttreatment setting. Clinical examination by a lymphedema therapist may include range of motion, muscle performance, circulation, sensation, hemodynamic monitoring, and functional mobility.

Survivors with lymphedema should also be assessed for distress (see "Anxiety, Depression, and Distress," available online, in these guidelines, at NCCN.org).

Treatment of Lymphedema

High-level evidence supporting treatments for lymphedema are lacking, and most studies have been performed in breast cancer survivors.[87–90] Most of the recommendations made by the panel are thus based on lower-level evidence, clinical experience, and expert consensus.

The oncology team should provide education regarding self-care management, including infection prevention measures, risk-reduction strategies, and maintenance of skin integrity on the affected side (see "Survivor Lymphedema Education," next section). Distress should be treated if present (see "Anxiety, Depression, and Distress," available in these guidelines at NCCN.org). Referral should be made to a certified lymphedema therapist, if available, for prescription and fitting of compression garments, performance of manual lymphatic drainage, and direction of supervised progressive resistance training. If a certified lymphedema therapist is not available, referral to an appropriate alternative provider for treatment should be considered.

Compression garments have been shown to reduce limb volume and are often used with other modalities such as manual lymphatic drainage.[90,91] Manual lymphatic drainage is performed by a specific massage technique designed to encourage lymph fluid to drain from the affected area. Systematic reviews and meta-analyses have assessed the efficacy of manual lymphatic drainage in breast cancer survivors with lymphedema and found that it can provide additional benefit when added to standard therapy.[92,93] In particular, compression bandaging alone leads to limb volume reductions of 30% to 39%, and manual lymphatic drainage appears to increase that reduction by an additional 7%.

Progressive resistance/weight training under supervision is recommended for survivors with lymphedema. Progressive resistance training and physical activity are not associated with exacerbation or development of lymphedema and may improve lymph-edema symptoms.[94–102] However, caution is advised in this population,[103] and survivors with or at risk for lymphedema should consider discussing physical activity plans with a lymphedema specialist before starting a program that involves strength or resistance training. Survivors with lymphedema should initiate strength training exercise involving the affected body part only if lymphedema is stable (ie, no need for lymphedema therapy within the past 3 months, no recent limb infections requiring antibiotics, no change in limb circumference >10%, no change in the ability to perform activities of daily living). Survivors should undergo baseline and periodic evaluation for development or exacerbation of lymphedema and should stop exercise and see a lymphedema specialist if exacerbation of lymphedema occurs. If a certified therapist is not available for supervision, survivors with lymphedema can perform resistance training with a professional trainer who has knowledge of cancer-related physical activity principles. Weights should be slowly progressed as tolerated, and lymphedema should be evaluated peri-odically. Most survivors with or at risk for lymphedema require compression garments during resistance training. The National Lymphedema Network has published a position statement with additional guidance for exercise in individuals with lymphedema.[101]

Survivor Lymphedema Education

Early detection and diagnosis is key for optimal lymphedema management because earlier stages are reversible. Therefore, survivors should be educated about the signs and symptoms of lymphedema and the importance of rapid reporting to the treatment team. Survivors should be told to inform their medical provider if subtle swelling or any other symptoms (eg, fullness, tightness, heaviness, pain) on the treated side are noted.

Survivors at risk for lymphedema and those with lymphedema are at a higher risk of localized infection in the affected area. These infections can require hospitalization for intravenous antibiotics. Therefore, survivors with or at risk for lymphedema should be educated to inform their medical provider immediately for signs of infection in the affected area. Risk of infections can be reduced by safe pet care and gardening techniques (See “Immunizations and Prevention of Infections,” page 1241). Survivors should also be educated on how to maintain skin in-tegrity with meticulous skin care of the affected area that includes avoidance of cuts, burns, skin irritants and allergens, insect bites, and pet scratches.[104,105] The use of moisturizing soaps and over-the-counter, fragrance-free emollients may also be helpful.[105]

Observational studies have shown that air travel, venipuncture, and blood pressure measurement (via arm cuff) are not associated with exacerbation or development of lymphedema, and precautionary measures are likely unnecessary.[74,76,85,86,106–109] For instance, in one study of 632 women with breast cancer prospectively screened for lymphedema with 3,041 arm volume measurements, no association was found between the development of lymphedema and blood draws, injections, or air travel.[86] In the absence of high-level data, however, the panel recommends that medical procedures such as venipunc-

ture and blood pressure measurements be done on the non–at-risk arm/limb if possible.[110] If necessary, procedures may be done using the at-risk arm/limb. More research is needed to determine the effect of these procedures on the risk of lymphedema.

Survivors should be informed that lymphedema is not a contraindication for physical activity and that no special precautions are required for cardiovascular/aerobic exercise or strength training of un-affected limbs.[94–96,98,99,103] In addition, continued full use of the involved extremity and range-of-motion exercises should be encouraged to maintain strength and range of motion even in the presence of lymphedema. Progressive resistance/weight training under supervision is recommended for patients with lymphedema, as discussed previously (see “Treatment of Lymphedema,” previous section). Exercise and physical therapy may also help prevent lymphede-ma symptoms. In the randomized controlled Lymphedema Education and Prevention study (CALGB 70305), women randomized to the education plus exercise arm self-reported greater range of motion at 12 months after lymph node dissection (a pre-specified secondary outcome) compared with women in the education-only arm (left, 91% vs 84%; P=.16; right, 90% vs 83%; P=.02).[111]

Surveillance of Survivors with Lymphedema

Survivors with lymphedema should have follow-up with the treatment team as clinically indicated. Clinicians should check range of motion, inquire about the fit and age of compression garments, replace compression garments if needed, and inquire about the performance of prescribed exercises and self-care management. Assessment for distress should also be performed as part of routine surveillance.

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 anticancer treatment.[112,113] In addition, survivors are at increased risk of complications from vaccine-preventable diseases, such as those caused by human papillomavirus and influenza viruses.[113,114]

Many infections in survivors can be prevented by the use of vaccines. However, data from the BRFSS found that 42% of survivors did not receive an influenza vaccination in 2009, and 52% reported never receiving a pneumococcal vaccination.[115] 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 noncancer control subjects.[116] A separate analysis of the SEER-Medicare database by another group found similar results.[117]

Vaccines represent a unique challenge in cancer and transplant survivors because they may or may not trigger the desired protective immune responses due to possible residual immune deficits.[118–120] In addition, certain vaccines, such as those that are live attenuated (eg, zoster [ZVL or VAR]; measles, mumps, rubella [MMR]), are contraindicated in actively immunosuppressed survivors because of an increased risk of developing the disease and/or prolonged shedding of 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 (eg, rituximab, alemtuzumab), 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. For information regarding antimicrobial prophylaxis, please see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (available online at NCCN.org).

Education:

Survivors should be educated about safe pet care, the avoidance of zoonosis, travel precautions, and gardening precautions.[121–126] Contact with pets did not increase the risk of fever, bacteremia, pneumonia, and gastroenteritis in children with acute myeloid leukemia,[127] and the panel believes that contact with pets is generally safe for most survivors. However, survivors should wash hands with soap and running water after handling animal feces. If possible, survivors at high risk for immune suppression should avoid direct contact with animal feces and other bodily secretions. Survivors with elevated risk of infection and those who are immunocompro-mised are at higher risk for zoonoses and should use extra caution and avoid contact with exotic animals (ie, snakes, turtles). Travel precautions include education on the need for pretravel vaccines, prophylaxis against specific infections, and education on how to prevent waterborne, airborne, and zoonotic infections.[128] Travelers may find useful information from the CDC (https://wwwnc.cdc.gov/travel/yellow-book/2018/advising-travelers-with-specific-needs/immunocompromised-travelers) or by 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.

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 immune-suppressive therapy (ie, chemotherapy or antibody-based therapy) at least 3 months before the planned vaccination. Patients receiving anti-estrogen or other hormone-modulating therapy do not have to delay vaccination for the completion of therapy. In general, the usual doses and schedules are

recommended, as outlined by the Advisory Committee on Immunization Practices (ACIP).[129] The Infectious Diseases Society of America (IDSA) has outlined guidance for vaccination in immunocompromised patients, including those with cancer and those post-HCT.[130] The NCCN Survivorship Panel outlined immunization guidelines specific to survivors of hematologic malignancies and solid tumors, with separate guidelines for survivors who have 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 white blood cell 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); tetanus, diphtheria, pertussis (Tdap); recombinant zoster (RZV) vaccine in all survivors 50 years or older; and human papillomavirus in previously unvaccinated survivors through age 26 years.[129] These vaccines do not contain live organisms; instead they contain inactivated organisms, purified antigens, bacterial components, or genetically engineered recombinant antigens. Whereas the effectiveness of these vaccinations might be suboptimal because of lingering immune suppression,[120] their administration is likely worth-while to achieve some protection in the absence of known harm.

Pneumococcal vaccine (PPSV-23/PCV-13) is recommended for all adults age 65 years or older and those at any age with immunocompromising conditions.[131,132] Pneumococcal vaccination is also recommended for survivors of lung cancer and those who had lung resection. Data from a population-based matched cohort study in Taiwan found that administration of PPSV-23 to ≥5-year survivors of cancer reduced hospitalization for pneumonia.[133] 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, functional or anatomic asplenia, or local epidemic/risks merit their use.

Live Viral Vaccines: Vaccines that contain live attenuated organisms (eg, live-attenuated influenza vaccine; MMR; live-attenuated ZVL, VAR, yellow fever vaccine) are contraindicated in actively immunocompromised survivors because of a proven or theoretical increased risk of disease and prolonged shedding of the live organism present in the vaccine. They should not be offered to actively immunocom-promised survivors, unless cleared by a clinician experienced in vaccine use or by an infectious disease specialist.

Live viral vaccines can be administered, however, to immunocompetent survivors 3 or more months after chemotherapy or 6 or more months after anti–B-cell antibody therapy, although consultation with an infectious disease specialist or clinician familiar with vaccination in

patients with cancer is strongly recommended. Live viral vaccines should not be administered to HCT survivors with active graft-versus-host disease (GVHD) or ongoing immunosuppression. They should only be administered to HCT survivors without active GVHD or ongoing immunosuppression after consultation with an infectious diseases specialist. For all survivors, when other vac-cine options exist, they are preferred over live-attenuated vaccines (eg, RZV).

Healthy immunocompetent individuals who live in a household with immunocompromised sur-vivors can receive the following live vaccines with caution: MMR, varicella zoster (VAR or ZVL), yellow fever, rotavirus, and oral typhoid vaccines.[130] Immunocompromised survivors should avoid contact with persons who develop skin lesions after receipt of VAR or ZVL until the lesions clear. In addition, immunocompromised survivors should avoid handling diapers of children who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination.

Influenza Vaccines: Annual influenza vaccination is recommended for all cancer and transplant survivors.[134] Live-attenuated influenza vaccines should be avoided in some survivors (see “Live Viral Vaccines,” previous section).[135] Therefore, preferred vaccines include inactivated influenza vaccines (ie, trivalent [IIV3] standard-dose, trivalent [IIV3] high-dose, and quadrivalent [IIV4] standard-dose) or recombinant influenza vaccine (ie, trivalent [RIV3] or quadrivalent [RIV4]).[129,135] Some evidence suggests that the high-dose IIV3 vaccine may provide better protection than standard-dose IIV3 in individuals 65 years or older.[136] No studies have addressed the superiority of any influenza vaccine in the cancer survivor population specifically. Administration of the influenza vaccine to survivors with egg allergy symptoms (other than hives) should be done at a center that can manage severe allergic reactions, as currently recommended for all individuals.[129]

Zoster (Shingles) Vaccine: A new recombinant zoster vaccine (RZV) has become available in the United States. The recombinant vaccine is the preferred zoster vaccine for cancer survivors, and is recommended for survivors aged ≥50 years.[137] In survivors who have previously received ZVL, immunization with RZV should be considered. The recombinant vaccine should not be given sooner than 2 months after administration of the live attenuated vaccine.

If RZV is unavailable or access to it is an issue, ZVL can be given as a single dose to survivors aged 60 years or older without active or ongoing immuno-deficiency, 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.[130,138] ZVL can also be considered for survivors aged 50 to 59 years with a history of VZV infection or VZV seropositivity with no previous doses of VAR vaccine if the recombinant vaccine is unavailable. ZVL should be avoided in immunocompromised survivors, but VAR can be considered in transplant survivors without active GVHD or enhanced immunosuppression 24 or more months after transplantation.

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Individual Disclosures for Survivorship Panel

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Gregory Broderick, MD	None	None	None	9/1/18
Wendy Demark-Wahnefried, PhD, RD	None	American Society of Clinical Oncology	None	7/10/18
Crystal S. Denlinger, MD, FACP	Agios Pharmaceuticals, Inc.; Array Pharmaceuticals; AstraZeneca Pharmaceuticals LP; BeiGene; Bristol-Myers Squibb Company; Eli Lilly and Company; Genentech, Inc.; MacroGenics, Inc.; MedImmune, Inc.; and Merrimack Pharmaceuticals	Bristol-Myers Squibb Company, and Merck & Co., Inc.	None	8/17/18
Debra L. Friedman, MD, MS	None	National Cancer Institute, and Rally Foundation	None	8/5/17
Mindy Goldman, MD	None	None	Madorra, Inc.	8/3/18
Melissa Hudson, MD	None	Pfizer Inc.	None	7/26/18
Nazanin Khakpour, MD, FACS	None	None	None	2/26/16
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Allison L. McDonough, MD	None	None	None	7/31/18
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Jeffrey Peppercorn, MD, MPH[a]	TG Therapeutics, Inc.	None	None	10/3/17
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Phyllis Zee, MD, PhD	Eisai Inc.; Harmony Biosciences; Jazz Pharmaceuticals Inc.; Philips; and Technogel	Eisai Inc.; Harmony Biosciences; Merck & Co., Inc.; Philips; and sanofi-aventis U.S.	None	8/2/18

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:
Michelle Melisko, MD: Merrimack Pharmaceuticals
Linda Overholser MD, MPH: Eli Lilly and Company
Jeffrey Peppercorn MD, MPH: GlaxoSmithKline

[b]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
Linda Overholser MD, MPH: Springer Publishing
Kathryn Ruddy MD, MPH: Merck & Co., Inc., and Pfizer Inc.

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