

New NCCN Guidelines[®] for Survivorship Care

Presented by Jennifer A. Ligibel, MD, and Crystal S. Denlinger, MD

Abstract

Survivorship is a stage in the cancer journey like diagnosis and treatment, but it tends to be somewhat neglected in the quiet afterthoughts of treatment completion. Although cancer recurrence, second cancers, and late side effects of treatment are major concerns for survivors, survivors also may experience a variety of long-term physical and psychological sequelae of a cancer diagnosis and treatment. Oncology professionals may be ill-prepared to tackle these topics, and they have few guidelines for meeting these patient needs. In this article, Dr. Jennifer A. Ligibel and Dr. Crystal S. Denlinger present highlights from the inaugural NCCN Clinical Practice Guidelines in Oncology on survivorship care, focusing on the subtopics of exercise, cognitive function, immunization, and sexual function. They also discuss implementing new recommendations on survivorship assessment in the clinic. (*JNCCN* 2013;11:640–644)

“The number of cancer survivors in the United States has been increasing fairly exponentially over the past 30 years or so,” said Jennifer A. Ligibel, MD, Assistant Professor, Department of Medicine, Harvard Medical School, and Senior Physician, Adult Oncology, Dana-Farber Cancer Institute, Boston. But survivorship care is still an often overlooked part of the continuum of cancer care, and many survivors and families are “lost in transition.”¹

Presented by Jennifer A. Ligibel, MD, Assistant Professor, Department of Medicine, Harvard Medical School, and Senior Physician, Adult Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, and Crystal S. Denlinger, MD, Assistant Professor and Attending Oncologist, Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania.

Dr. Ligibel has disclosed that she has no financial interests, arrangements, or commercial interest conflicts with the manufacturers of any products discussed in this article or their competitors. Dr. Denlinger has disclosed that she receives research support from AstraZeneca Pharmaceuticals LP; MedImmune Inc.; and Merrimack Pharmaceuticals.

Correspondence: Jennifer A. Ligibel, MD, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115. E-mail: jligibel@partners.org

Crystal S. Denlinger, MD, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111. E-mail: crystal.denlinger@fccc.edu

To better address the issues faced by cancer survivors and their families and to offer practical recommendations for oncology health care teams to implement in the clinic, NCCN created NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on survivorship care. “They are intended as a library of tools for a provider to use when assessing and treating a cancer survivor,” reported Crystal S. Denlinger, MD, Assistant Professor and Attending Oncologist, Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, and Chair of the NCCN Survivorship Panel. Considering the current heterogeneity in how survivorship care is delivered across the country, these guidelines could help provide a framework for the delivery of that care in the future, added Dr. Ligibel, who is also a member of the NCCN Survivorship Panel.

Navigating the Realm of Survivorship Care

Cancer survivors are a heterogeneous group with different needs, noted Dr. Ligibel, and optimal care differs along the cancer care continuum. According to a comprehensive report by the IOM in 2005,¹ the essential components of survivorship care center on prevention, surveillance, intervention, and coordination (Table 1). To properly provide comprehensive long-term care of the cancer survivor, a provider needs certain critical information, including a summary of the treatment a survivor received, potential side effects of cancer treatment, a schedule of follow-up visits and surveillance plan, tips for maintaining a healthy lifestyle and preventing recurrent or new cancers, and the availability of psychological and social support services.¹

However, the IOM report acknowledged the lack of clear guidelines and training for oncology health care professionals in the realm of survivorship care.¹ In addition,

Table 1 Essential Components of Survivorship Care

Prevention	Recurrent, new cancers, late effects
Surveillance	Recurrence, second cancers Medical and psychosocial late effects
Intervention (and Support)	Consequences of disease and treatment, provide updates, foster adherence
Coordination	Between providers to ensure health needs are met

IOM Report: From Cancer Patient to Cancer Survivor: Lost in Transition. Committee on Cancer Survivorship: Improving Care and Quality of Life, 2005. The National Academies Press.

tion, recent reports have shown that many concerns of cancer survivors are not being met.² In general, oncologists tend to adequately address physical concerns, but emotional and practical concerns may not receive as much attention, added Dr. Ligibel.

To further address this apparent gap, the inaugural NCCN Guidelines on survivorship care focused on the “vast and persistent impact both the diagnosis and treatment of cancer have on the adult survivor.” Subtopics included in the Guidelines are anxiety and depression, cognitive function, exercise, immunizations/infections, fatigue, pain, sexual function, and sleep disorders. The select subtopics presented by Drs. Ligibel and Denlinger were exercise, cognitive function, immunization, and sexual function. The other subtopics have been adapted from existing NCCN Guidelines. “These survivorship guidelines are meant to be a companion to the disease guidelines,” explained Dr. Ligibel, “and used to provide guidance in the management of common effects of cancer and its treatment.”

The Benefits of Exercise Extend to Cancer Survivors

A great deal of observational data suggests that exercise offers many benefits to cancer survivors. Dr. Ligibel reviewed representative studies on the role of exercise in survivors of the 3 most common malignancies: breast, colorectal, and prostate cancers.

A number of studies illustrate the connection between physical activity and disease outcomes in cancer survivors.^{3,4} Ballard-Barbash et al³ systematically reviewed the literature from 1950 to 2011 related to physical activity and cancer survival. They noted that women who exercised had consistently lower breast cancer-specific and overall mortality than did less active individuals, stated Dr. Ligibel. The large-scale,

prospective 30-year Nurses’ Health Study included nearly 3000 women with breast cancer⁴ and showed 50% fewer cancer recurrences and lower overall mortality in the women who exercised more than 3 hours per week than in those who did not.

A similar link between exercise and prognosis was noted in a study of patients with stage III colon cancer.⁵ Beyond surgical re-

section and postoperative adjuvant chemotherapy, exercise was associated with a reduced risk of both cancer recurrence and mortality in this group of 832 patients. In a more recent study involving 1455 men diagnosed with clinically localized prostate cancer, men who walked at a brisk pace for at least 3 hours per week showed a 57% lower risk of disease progression than men who walked more slowly for less time.⁶

Therefore, the NCCN Guidelines recommend that all patients be encouraged to be physically active and to return to daily activities as soon as possible after treatment, though recommendations for activity must be tailored to the individual’s abilities and preferences. Dr. Ligibel noted that the NCCN Guidelines endorse recommendations similar to the American Cancer Society and American College of Sports Medicine: at least 150 minutes of moderate-intensity activity per week coupled with strength training and stretching at least 2 or more times per week.

The NCCN Guidelines also include an assessment pathway for individualizing exercise recommendations. The risk for exercise-induced adverse events should be evaluated, with the use of support services such as physical therapy and exercise specialists for those patients deemed to be high risk for events. Practical advice for specific populations (such as those with lymphedema, transplant, ostomy, peripheral neuropathy, and bone loss or metastases) is provided. In addition, examples of light, moderate, and vigorous exercise are listed, and strategies to increase physical activity are offered for both survivors meeting exercise guideline recommendations and those who are not.

Thinking Clearly About Cognitive Dysfunction

“We struggled with the topic of cognitive function a bit as a panel, because it has been so ill-defined,” admitted

Ligibel and Denlinger

Dr. Ligibel. Although cognitive dysfunction primarily manifests as problems with memory, other issues with executive function, learning, and processing speed have been noted, she added. The International Cognition and Cancer Task Force offered the following definition of cognitive impairment: “a frontal, subcortical toxicity profile, with cognitive dysfunction within domains of information and processing speed, attention, memory retrieval, and executive function.”⁷

Patients at high risk of cognitive decline include those with primary central nervous system tumors or brain metastases. However, Dr. Ligibel noted the difficulty in determining the scope of the problem. Studies have reported that 19% to 78% of patients experienced cognitive difficulties after treatment for breast cancer or lymphoma.⁸ This wide range “points to the problems with this research,” she admitted.

Managing cognitive dysfunction in cancer survivors presents several challenges. For instance, lack of a standard definition and sensitive assessment tools complicate the assessment process. The pathophysiology of cognitive decline can also be unclear in these patients, and minimal research has been performed on preventive and treatment strategies, stated Dr. Ligibel. Finally, many patients may report difficulties with memory and processing before undergoing chemotherapy.

Growing evidence supports the validity of patient-reported experiences of cognitive dysfunction associated with cancer treatment. However, evidence to guide management of this condition is limited, especially for cancers other than breast. The NCCN Guidelines include a pathway for evaluating cognitive function, which indicates the need to screen for reversible contributing factors (especially medication side effects, anxiety, depression, and fatigue). Assessment starts with a focused history; imaging or neuropsychologic evaluation is suggested if focal neurologic deficits are found or if the patient is at high risk of metastatic disease or a primary brain tumor. Practical interventional strategies center on patient and family education and counseling, with some recommendations for pharmacologic interventions if necessary.

Appropriate Vaccinations for Cancer Survivors

Cancer survivors may be at an elevated risk of infection as a result of their treatment, and they may not

be receiving adequate immunization, stated Dr. Denlinger. For instance, Locher et al⁹ found that older adult cancer survivors received influenza vaccination at lower rates than matched controls despite health care interactions.

Therefore, the NCCN Guidelines on survivorship recommend that adults with or after cancer receive appropriate vaccination based on their age and medical condition as part of standard practice. Vaccines considered to be safe for cancer and transplant survivors and close contacts are inactivated or purified antigens or bacterial components, including for influenza, pneumonia, meningitis, and hepatitis. Vaccines that are contraindicated or to be used with caution in these patients include live attenuated vaccines, such as for measles, mumps, rubella, and herpes zoster.

Another important recommendation is to vaccinate patients at least 3 weeks before the start of cancer treatment if possible. In this way, “patients can get the full benefit of immunity,” explained Dr. Denlinger. However, clinically appropriate vaccinations should not be withheld if a patient is currently undergoing treatment. Assessment guidelines for vaccination encompass disease status, prior and current treatment, time from treatment completion, exposure to endemic infections or epidemics, and overall immune system viability (ie, white blood cell counts within normal limits and off immunosuppressive medications). Finally, principles regarding the use of the zoster (shingles) vaccination in cancer or transplant survivors are provided.

Sexual Dysfunction: A Common and Underreported Problem

Sexual dysfunction has been reported in up to 90% survivors of prostate cancer, 75% of survivors of rectal cancer, and 50% of survivors of breast and gynecologic cancer, according to Dr. Denlinger. Causes can include chemotherapy, surgery, radiotherapy, and hormonal therapies. Although it can cause distress and affect quality of life, patients do not generally receive help for sexual dysfunction, and physicians often do not know how to talk about it with their patients, acknowledged Dr. Denlinger. This multifactorial problem may incorporate psychological, physiologic, and sociologic elements.¹⁰ Some symptoms are sex-specific, such as erectile dysfunction

tion for men and dyspareunia and vaginal atrophy for women; however, loss of libido, infertility, negative body image, and partner distress may be common to both sexes.¹¹

General assessments for sexual dysfunction in cancer survivors should focus on the level of activity (past and present), the impact of cancer therapy, and sexual concerns or symptoms. Comorbidities, risk factors, and psychosocial factors should be considered.

The NCCN Guidelines feature validated tools for assessment, including a brief sexual symptom checklist for women and a sexual health inventory for men (SHIM). Suggestions for additional gender-specific evaluation and problem-based treatment recommendations are provided. An integrative biopsychosocial model for intervention for cancer-related sexual problems illustrates the complex factors at play (Figure 1).¹¹ “We tried hard to minimize the interventions to things an oncology or primary care provider could do versus things that need to

be referred to other providers,” explained Dr. Denlinger, “to provide clinicians with tools necessary to address this important and undertreated sequelae of cancer and treatment.”

Implementation of Guidelines: From the Panel to the Clinic

Both Dr. Ligibel and Dr. Denlinger admitted that incorporating these guidelines into everyday practice may be challenging initially, particularly in regard to time and staff. However, baseline tools provided in the NCCN Guidelines for Survivorship are intended to ease the process.

Dr. Denlinger recommends assessing survivorship issues at regular intervals using standardized questionnaires to evaluate symptoms if possible. Queries should be made about the late and long-term effects of cancer and its treatment, receipt of preventive health services, and health behaviors. Patients should undergo periodic reassessment to identify the develop-

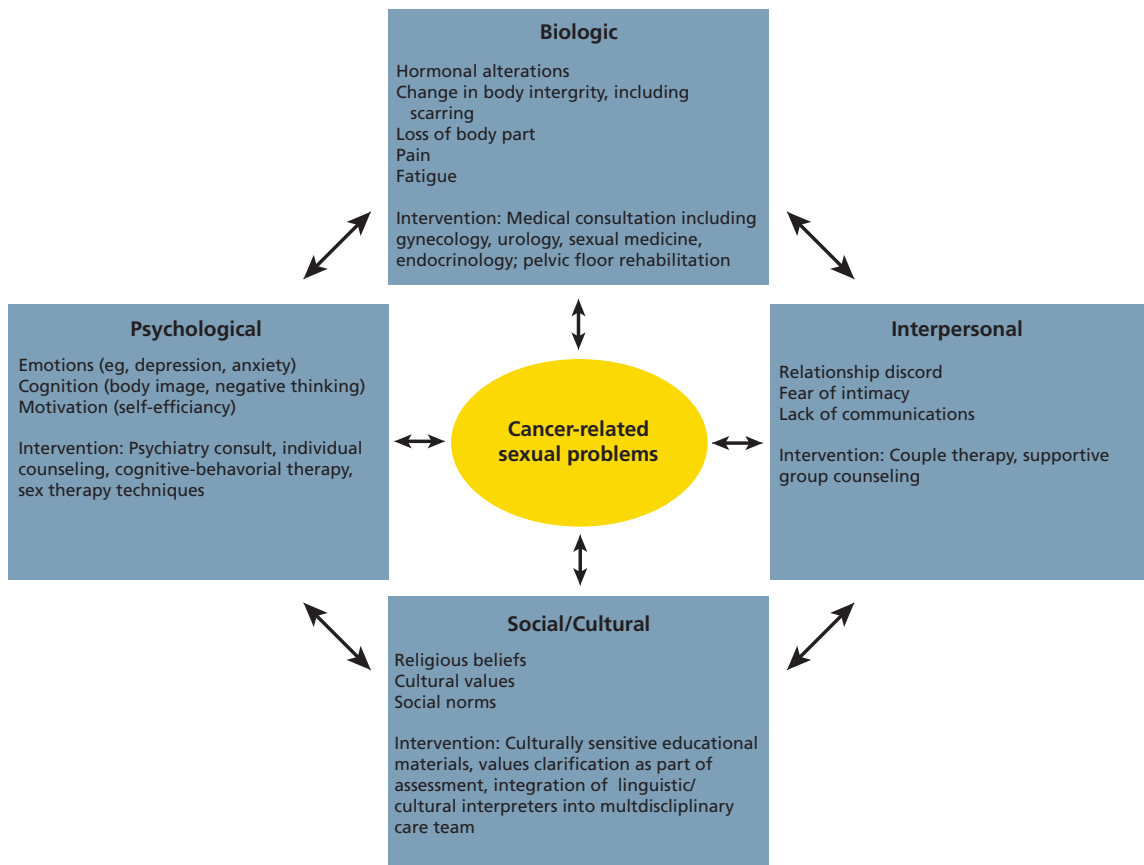


Figure 1 Integrative biopsychosocial model for intervention for cancer-related sexual problems. Reprinted with permission. © 2012 American Society of Clinical Oncology. All rights reserved. Bober SL, Varela VS: J Clin Oncol 2012;30:3712-3719.

Ligibel and Denlinger

ment of new effects. The NCCN Guidelines use what Dr. Denlinger called “a quick screening assessment,” which opens the discussion of a host of survivorship concerns through a few simple questions.

In addition to regular assessments, routine discussion between health care providers and cancer survivors regarding posttreatment effects, healthy lifestyle behaviors, and receipt of preventive care is important. Although a survivorship care plan is endorsed by NCCN, it is not required. “We recognize that not everyone has the time or staff to generate and then employ a survivorship care plan in everyday practice,” admitted Dr. Denlinger.

The NCCN Guidelines for Survivorship are meant for both primary care and oncology professionals, as both play a role in the continued care of cancer survivors. They are not intended to replace existing disease-specific guideline recommendations for cancer surveillance. This reference source for survivorship-related issues will be updated regularly, with plans to add additional guidelines for common effects of cancer and its treatment in future versions.

References

1. Institute of Medicine (IOM). *From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington DC: The National Academies Press; 2005.
2. Rechis R, Arvey SR, Beckjord EB. Perspectives of a lifelong cancer survivor: improving survivorship care. *Nat Rev Clin Oncol* 2013;10:117–120.
3. Ballard-Barbash R, Friedenreich CM, Courneya KS, et al. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst* 2012;104:815–840.
4. Holmes MD, Chen WY, Feskanich D, et al. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005;293:2479–2486.
5. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol* 2006;24:3535–3541.
6. Richman EL, Kenfield SA, Stampfer MJ, et al. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. *Cancer Res* 2011;71:3889–3895.
7. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol* 2011;12:703–708.
8. Wefel JS, Schagen SB. Chemotherapy-related cognitive dysfunction. *Curr Neurol Neurosci Rep* 2012;12:267–275.
9. Locher JL, Rucks AC, Spencer SA, et al. Influenza immunization in older adults with and without cancer. *J Am Geriatr Soc* 2012;60:2099–2103.
10. Krychman M, Millheiser LS. Sexual health issues in women with cancer. *J Sex Med* 2013;10(Suppl 1):5–15.
11. Bober SL, Varela VS. Sexuality in adult cancer survivors: challenges and intervention. *J Clin Oncol* 2012;30:3712–3719.