Management of Unexplained Symptoms in Survivors of Cancer

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Abstract

Quality health care for survivors of cancer must evaluate and manage symptoms that are reported at the surveillance visit but are not linked to a cancer recurrence or a new cancer. At present, this does not always occur. This article analyzes quality of health care for survivors of cancer, taking empirical evidence and clinical expertise into consideration. Although emotional distress on the part of the survivor of cancer may exacerbate or

even explain the presence of experienced symptoms, there are other potential explanations as well. When survivors present with persistent symptoms (even if unexplained) after cancer diagnosis and treatment, the symptoms can impact the survivor's function and well-being. Oncologists and other providers need to assess and directly target these symptoms for appropriate triage to those who can best help these survivors reduce the symptoms and their impact.

Introduction

After primary treatment for cancer, many survivors experience symptoms that can impact function and well-being for years.^{1,2} These patients are often counseled to pay attention to symptoms (eg, change in pain) as potential signs of recurrence or of some new form of cancer. This can create a situation in which variations of these symptoms motivate a follow-up visit as a result of concern about a possible recurrence or a new tumor. When the findings of the visit do not indicate any change in tumor pathology, the visit often terminates with the survivors being told that they should continue to be watchful of the symptoms, but that they are fine.

When these symptoms persist without evidence of pathology, they may be placed in the widely used category of unexplained symptoms,³ which are defined as “symptoms for which no objective physical or pathological changes can be found.”⁴ These symptoms may be seen as manifestations of distress.⁵ However, although distress can exacerbate many of these symptoms,⁶ an exclusive focus on distress is not the only option providers and survivors of cancer have. Direct attention to the symptom and focus on its impact on function may lead to better overall outcomes. Application of concepts developed to manage treatment of patients with persistent unexplained symptoms for non-life threatening diseases⁷ may not be appropriate for persistent symptoms in those with life-threatening diseases such as cancer. Historically, unexplained symptoms in the oncology setting have been understandably relegated to a lower priority problem, despite the impact they may have on recovery of optimal health.⁸

Although it may be understandable to put a lower priority on symptoms that do not indicate a recurrence because of the acute nature of the disease, there may also be a subtle bias operating when survivors with cancer present symptoms that do not reflect tumor activity. Such a situation places many problems in the unexplained category, and they are often not consistently followed up on. This unexplained category of symptoms may include long-term or late effects but is specific to symptoms that lack clear, conventional support from medical tests. Therefore, whereas long-term or late effects are typically

evidenced by direct confirmation, unexplained symptoms have no objective physical or pathologic basis. As a result, direct efforts to manage these symptoms may not be given. However, these symptoms are often a genuine concern for patients because they can impact function or quality of life.^{9,10} When such symptoms are relegated to being considered a less important matter, many survivors are left to their own resolve to search for evaluation and treatment for these troublesome symptoms. Providers should take a step back and look more closely at these symptoms when they impact important dimensions of health.¹¹

Symptoms in Survivors of Cancer?

Not all survivors of cancer experience the same unexplained symptoms. We limit coverage to the symptoms that are most frequently addressed in the oncology and survivorship literature. Some survivors report clusters of symptoms, such as pain, fatigue, mood changes, and sleep disturbance.¹² At times, a medical evaluation or an understanding of the cancer and its treatment can help explain these symptoms, but often this is not the case. Although many symptoms generally improve over time, they do not always completely remit.^{13,14} These symptoms can vary according to cancer type, time from primary treatment, new comorbidities not related to cancer or its treatment, and medical and psychosocial factors.¹⁵ There are many reviews of symptoms in survivors of cancer^{16,17}; however, it is important to acknowledge that these symptoms can persist for 10 years after diagnosis and treatment.^{1,16,18}

Epidemiology of Recurrent and New Tumors

Clinical practice and research indicate that there is a risk for recurrence of the original cancer as well as new forms of malignancies.¹⁹ Both possibilities are on the minds of survivors of cancer²⁰ and many providers.²¹ The days of blindly following projections of 5-year survival rates are rapidly dwindling as survivors live longer and a more informed view of the natural history of the various types of this disease is unveiled.¹⁹ It is recognized that these estimates may not provide a valid assessment of mortality, given the continuous enhancements in early detection and treatment during the past few decades.²² Mor-

bility is another open-ended feature of survivorship as well. Survivors of cancer must stay vigilant for signs of cancer recurrence or new tumors. However, these signs are often the symptoms they report in the absence of tumor pathology. When these symptoms are related to optimal function or well-being, as they often are,²³ they must be attended to.

Concepts of Unexplained Symptoms

In the past half-century, explanations for a persistent focus on symptoms such as maladaptive perceptions or abnormal reactions have joined the ranks with hypochondriasis, which is defined as “a persistent fear or belief that one has a serious, undiagnosed medical illness.”²⁴ p1464 Over the years, attempts to treat hypochondriasis and the accompanying symptoms have targeted reducing the fear of illness and altering the patient’s belief system, which plays an essential role in a patient’s focus on symptoms. The only randomized clinical trial designed to treat hypochondriasis indicated that, although the intervention was associated with an attenuation in health-related anxiety and frequency of hypochondriacal thoughts, there was no concomitant change in reported symptoms.²⁴ This is supported by meta-analytic findings that suggest that although many unexplained symptoms are related to anxiety and depression, they are not completely dependent on them.²⁵ Therefore, it is important to address the symptoms themselves in addition to any distress when no traditional markers of pathology exist.

Another way symptoms in the absence of definitive pathology have been historically explained is through the concept of catastrophizing. The term refers to a cognitive coping process “characterized by negative self-statements and overly negative thoughts and ideas about the future.”²⁶ p51 Even after accounting for initial levels of pain and disability, catastrophizing is related to severity of symptoms.²⁶ The concept has also been applied to survivors of cancer. A systematic literature review noted that three of the four examined studies that included measures of catastrophizing in survivors found that catastrophizing was correlated with more intense cancer pain.²⁷ This response to symptoms has also been found to be more closely related to higher levels of fatigue in patients with breast cancer receiving radiation therapy than for those receiving chemotherapy alone.²⁸ This suggests an increased susceptibility to subjective interpretations of fatigue in those receiving radiation.

Although anxiety or depressive symptoms can exacerbate and/or prolong symptoms, reducing distress does not consistently or totally eliminate the symptoms.²⁹ When a survivor of cancer is told the symptoms are not signs of a recurrence or a new cancer, a feeling of relief may attenuate symptoms, even though symptoms have not changed. However, in some survivors of cancer, these problems can and do persist.

Figure 1. Flow chart for management of unexplained symptoms in survivors of cancer.

What Can Be Done Now?

Although the symptoms of survivors of cancer may result in part from distress, it is also plausible that the symptoms have been precipitated by cancer and its treatment. In such a situation, there is a critical role for oncology, primary care, nutrition, rehabilitation, and the behavioral health specialties not only to modify maladaptive perceptions or cognitions but also to help facilitate resilience and symptom management. Not only do we need educational training for providers, but we also need fiscal realignment to deliver such care.³⁰ Never before in the history of the war on cancer have we had such a large number of individuals living with long-term and late effects. Referral to an entire cadre of health care providers (eg, physical therapists, nutritionists, acupuncturists, behavioral health specialists) to assist in the everyday management of survivors of cancer is essential. By using appropriate referrals, survivors can receive more specialized care for their symptoms.³¹ Having better control over the symptoms, through referral to the appropriate providers, may also assist in alleviating survivors’ fears concerning the symptoms.

Figure 1 depicts a decision tree for evaluating these symptoms. When evidence of a tumor exists, treatment can follow the standard of care. However, when no evidence exists, it is important to evaluate further. This evaluation would include a direct targeting of the presenting symptoms. The health care provider should address any impact on function and any consequences that these symptoms have on well-being. If the patient’s function has been impacted in a negative manner (eg, decrease in endurance, limited strength), referrals can be made to address these complaints. Physical therapists, nutritionists, and vocational therapists, among others, are all qualified to help a survivor of cancer regain function. If the patient’s well-being is negatively impacted by symptoms (eg, distress, lack of social

support), there are still other referrals that may benefit the patient. Psychotherapy or support groups may assist the survivor in learning to cope with his or her symptoms in a more effective manner. A case example of using this decision tree to assist a patient is provided below.

Case example. Cindy, a 53-year-old survivor of breast cancer, recently began experiencing fatigue again while at work and performing household chores. Although Cindy, who completed primary treatment 3 years before and is currently on adjuvant hormonal therapy, has consistently had clear mammograms, she is now worried that the fatigue is somehow indicative of a cancer recurrence. Her fatigue is currently getting in the way of work and family life.

Cindy's doctor performed a mammogram and did a comprehensive work-up. The doctor reported that the cancer had not returned and that there were no other indications that the fatigue was caused by a medical condition. However, when he questioned Cindy on the ways in which her fatigue was interfering with her life, he determined that the fatigue had functional and well-being implications. He explained that there were many options for her that may help reduce her fatigue. He started Cindy on a month-long trial of 200-mg modafinil, a medication that has shown some positive effects on cancer-related fatigue in certain survivors of breast cancer.³² Because of the benefits of exercise,³³ he also encouraged Cindy to join a gym. As an additional measure, he referred Cindy to an acupuncturist³⁴ with whom she was able to address her fatigue and other health and stress-related concerns in appointments two times per week. After a few weeks of incorporating the recommended changes into her routine, Cindy began to notice her fatigue dissipating.

In this scenario, Cindy's doctor attended to her concerns and made necessary referrals. Although each of the interventions recommended to Cindy may not completely ameliorate her fatigue, her symptoms can be attenuated, and she feels as

though her medical concerns have been addressed; she now has more trust and faith in her provider.

Survivors of cancer with persistent symptoms should not be left to accept the symptoms, consider them unexplained, or search for help on their own. Providers can assist these survivors in their efforts at long-term optimization of health, function, and well-being by simply making appropriate referrals when unexplained symptoms negatively impact the survivor.

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References

- Helgeson VS, Tomich PL: Surviving cancer: A comparison of 5-year disease-free breast cancer survivors with healthy women. *psychooncology* 14:307-317, 2005
- Bower JE, Ganz PA, Desmond KA, et al: Fatigue in long-term breast carcinoma survivors: A longitudinal investigation. *Cancer* 106:751-758, 2006
- Haylock PJ, Mitchell SA, Cox T, et al: The cancer survivor's prescription for living. *Am J Nurs* 107:58-70, 2007
- Aggarwal VR, McBeth J, Zakrzewska JM, et al: The epidemiology of chronic syndromes that are frequently unexplained: Do they have common associated factors? *Int J Epidemiol* 35:468-476, 2006
- Burton C: Beyond somatisation: A review of the understanding and treatment of medically unexplained physical symptoms (MUPS). *Br J Gen Pract* 53:231-239, 2003
- Sharp TJ, Harvey AG: Chronic pain and posttraumatic stress disorder: Mutual maintenance? *Clin Psychol Rev* 21:857-877, 2001
- Hatcher S, Arroll B: Assessment and management of medically unexplained symptoms. *BMJ* 336:1124-1128, 2008
- World Health Organization: Preamble to the Constitution of the World Health Organization. Presented at the International Health Conference, New York, NY, June 19-22, 1946
- Zebrack BJ, Zeltzer LK: Quality of life issues and cancer survivorship. *Curr Probl Cancer* 27:198-211, 2003
- Janz NK, Mujahid M, Chung LK, et al: Symptom experience and quality of life of women following breast cancer treatment. *J Womens Health (Larchmt)* 16:1348-1361, 2007
- U.S. Department of Health and Human Services: Healthy People 2010: Understanding and improving health (ed 2). <http://www.feddesk.com/freehandbooks/121505-1.pdf>
- Cleeland CS, Mendoza TR, Wang XS, et al: Assessing symptom distress in cancer patients: The M. D. Anderson Symptom Inventory. *Cancer* 89:1634-1646, 2000
- Anderson-Hanley C, Sherman ML, Riggs R, et al: Neuropsychological effects of treatments for adults with cancer: A meta-analysis and review of the literature. *J Int Neuropsychol Soc* 9:967-982, 2003 Nov
- Härter M, Reuter K, Aschenbrenner A, et al: Psychiatric disorders and associated factors in cancer: Results of an interview study with patients in inpatient, rehabilitation and outpatient treatment. *Eur J Cancer* 37:1385-1393, 2001
- Zebrack BJ, Gurney JG, Oeffinger K, et al: Psychological outcomes in long-term survivors of childhood brain cancer: A report from the childhood cancer survivor study. *J Clin Oncol* 22:999-1006, 2004
- Burkett VS, Cleeland CS: Symptom burden in cancer survivorship. *J Cancer Surviv* 1:167-175, 2007
- Aziz NA: Cancer survivorship research: Challenge and opportunity. *J Nutr* 132:3494S-3503S, 2002 (suppl)

18. Mao JJ, Armstrong K, Bowman MA, et al: Symptom burden among cancer survivors: Impact of age and comorbidity. *J Am Board Fam Med* 20:434-443, 2007
19. Brown LM, Chen BE, Pfeiffer RM, et al: Risk of second non-hematological malignancies among 376,825 breast cancer survivors. *Breast Cancer Res Treat* 106:439-451, 2007
20. Mehnert A, Berg P, Henrich G, et al: Fear of cancer progression and cancer-related intrusive cognitions in breast cancer survivors. *Psychooncology* 18:1273-1280, 2009
21. Cheung WY, Neville BA, Cameron DB, et al: Comparisons of patient and physician expectations for cancer survivorship care. *J Clin Oncol* 27:2489-2495, 2009
22. Brewster AM, Hortobagyi GN, Broglio KR, et al: Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst* 100:1179-1183, 2008
23. Hansen JA, Feuerstein M, Calvio LC, et al: Breast cancer survivors at work. *J Occup Environ Med* 50:777-784, 2008
24. Barsky AJ, Ahern DK: Cognitive behavior therapy for hypochondriasis: A randomized controlled trial. *JAMA* 291:1464-1470, 2004
25. Henningsen P, Zimmermann T, Sattel H: Medically unexplained physical symptoms, anxiety, and depression: A meta-analytic review. *Psychosom Med* 65:528-533, 2003
26. Keefe FJ, Brown GK, Wallston KA, et al: Coping with rheumatoid arthritis pain: Catastrophizing as a maladaptive strategy. *Pain* 37:51-56, 1989
27. Zaza C, Baine N: Cancer pain and psychosocial factors: A critical review of the literature. *J Pain Symptom Manage* 24:526-542, 2002
28. Jacobsen PB, Andrykowski MA, Thors CL: Relationship of catastrophizing to fatigue among women receiving treatment for breast cancer. *J Consult Clin Psychol* 72:355-361, 2004
29. Lackner J, Jaccard J, Krasner S, et al: How does cognitive behavior therapy for irritable bowel syndrome work? A mediational analysis of a randomized clinical trial. *Gastroenterology* 133:433-444, 2007
30. Blaauwbroek R, Zwart N, Bouma M, et al: The willingness of general practitioners to be involved in the follow-up of adult survivors of childhood cancer. *J Cancer Surviv* 1:292-297, 2007
31. Gilchrist LS, Galantino ML, Wampler M, et al: A framework for assessment in oncology rehabilitation. *Phys Ther* 89:286-306, 2009
32. Morrow GR, Gillies LJ, Hickok JT, et al: The positive effect of the psychostimulant modafinil on fatigue from cancer that persists after treatment is completed. *J Clin Oncol* 23:732s, 2005 (suppl; abstr 8012)
33. Mustian KM, Morrow GR, Carroll JK, et al: Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue. *Oncologist* 12(Suppl 1):52-67, 2007
34. Molassiotis A, Sylt P, Diggins H: The management of cancer-related fatigue after chemotherapy with acupuncture and acupressure: A randomised controlled trial. *Complement Ther Med* 15:228-237, 2007

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