Health-Related Quality of Life:

The Impact on Morbidity and Mortality

Andrea Sitlinger, MD[a] and **Syed Yousuf Zafar, MD, MHS**[b,*]

[a]Hematology and Oncology, Duke University Medical Center, 2424 Erwin Road, Suite 602, Room 6046, Durham, NC 27705, USA

[b]Duke Cancer Institute, Sanford School of Public Policy, 2424 Erwin Road, Suite 602, Room 6046, Durham, NC 27705, USA

Keywords

INTRODUCTION

In the age of ever-expanding treatments and precision medicine, the hope for cure remains the ultimate goal for patients who have cancer and their providers. Equally important to many patients is the quality of life (QOL) achieved during and after treatment. Health-related QOL (HRQOL) is generally accepted as a multidimensional assessment of how disease and treatment affect a patient's sense of overall function and wellbeing.[1] The US Food and Drug Administration (FDA) officially defines HRQOL as "a multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life."[2] HRQOL is among the accepted primary outcomes in cancer trials for the FDA owing to its recognized importance to patients.

A primary reason for the emphasis on HRQOL, even at the drug-approval level, is that, beyond the general principle of wanting patients to live well and longer, HRQOL is increasingly acknowledged as crucial to patient overall outcomes. Quinten and colleagues[3] conducted a meta-analysis of the European Organization for Research and Treatment of Cancer (EORTC) clinical trials to examine this question. The EORTC Quality of Life Questionnaire (QLQ)-C30 is among the most used validated HRQOL questionnaires. It consists of 30 questions along with disease-specific versions (eg, breast, prostate, multiple myeloma). Quinten and colleagues[3] reviewed 30 randomized controlled trials that used the EORTC measure and evaluated survival data. Eleven different cancer diagnoses were identified: esophageal, pancreas, ovarian, testicular, breast, head and neck, prostate, brain, lung, colorectal, and melanoma. The investigators found that physical functioning, pain, and appetite loss as measured by the EORTC QLQ-C30 were statistically significant prognostic

*Corresponding author. yousuf.zafar@duke.edu.

variables. Moreover, when these categories were combined, overall survival prognostication was 6% more accurate than when using sociodemographic (eg, age) and clinical characteristics (eg, metastatic disease state) alone.

Furthermore, Epplein and colleagues[4] examined QOL in relation to survival in 2230 survivors of breast cancer. They found that women in the top one-third of social wellbeing by QOL score had a 38% decreased risk of mortality compared with the bottom third at 6 months. Also, they found a 48% decreased risk of breast cancer recurrence when comparing the top third and bottom thirds of the social wellbeing QOL score. Of note, although this was statistically significant at 6 months, there was no difference in QOL at 36 months. The investigators concluded that the first year of social wellbeing after diagnosis was most likely to be associated with recurrence and mortality.

Another study in subjects with head and neck cancer used the EORTC measure and developed a general sum score with a hazard ratio (HR) of 5.15 that was predictive of survival.[5] In looking at the individual components of the EORTC measure, McKernan and colleagues[6] found that in subjects with gastroesophageal cancer who received surgery with either a curative intent or palliative treatment, physical functioning, physical symptoms (eg, appetite loss, constipation, fatigue), cognitive function, social functioning, role function, and global QOL were all significantly associated with cancer-specific survival on univariate analysis. Similarly, Braun and colleagues[7] found that multiple components of the EORTC QLQ-C30 scale, such as physical function, social function, emotional parameters, and physical symptoms, predicted survival in univariate analysis in prostate cancer. Braun and colleagues[8] also examined the EORTC QLQ-C30 in relation to non-small cell lung cancer and found that every 10-point increase in global QOL was associated with a 9% increase in survival and that a 10-point increase in physical function was associated with a 10% increase in survival.

Thus, evidence suggests that overall QOL is important to patients and plays a role in determining outcomes in patients with cancer. This article examines components of HRQOL and cancer treatment, including the (1) physical, (2) psychosocial, and (3) financial burdens. It examines how these components of HRQOL affect patients' overall wellbeing and survival.

PHYSICAL BURDEN

The physical symptoms related to cancer and associated treatments are traditionally the most recognized and studied of the QOL components. Patients will often reference physical symptoms when discussing QOL concerns as they relate to treatment options.

Assessing the burden of these symptoms is essential. Many validated tools assess physical symptoms in relation to QOL, such as the physical symptom portion of the EORTC measure (see previous discussion). Another common tool is the Functional Assessment of Cancer Therapy (FACT). FACT-General (G) assesses psychosocial and functional levels.[9] This measure has an advantage compared with more general HRQOL measures in that it has been expanded to address specific symptoms of numerous cancer diagnoses, as well as symptoms

related to specific treatment (eg, neurotoxicity assessment and bone marrow transplant assessment), in more than 70 languages. For instance, the FACT–Lung Cancer Symptom (LCS) Index addresses specific lung or breathing symptoms,[10] whereas the FACT-Colorectal (C) Symptom Index addresses bowel issues in more detail.[11] Although numerous tools now exist for specific disease states and symptoms, the FACT surveys often serve as validation benchmarks for newer measures. With validated tools for QOL assessment, patients' symptoms can be methodically addressed. In addition, QOL can be understood in the context of other outcomes, such as prognosis and mortality.

General physical symptom burden has certainly been linked to prognosis and survival. The Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Score (KPS) have been used in oncology for years to help assess functional status and discern treatment options.[12] These scores, however, reflect physicians' assessments of patient's physical function rather than patients' own assessment of symptom severity. More objective measures of physical function based on patients' own reports of symptoms have been developed, and several studies have found that these patient-reported measures of physical symptom burden are even more strongly correlated with survival.

Reck and colleagues[13] evaluated performance status and QOL in subjects with extensive-stage small cell lung cancer. They found that among subjects who reported lower FACT-G scores, patients with higher FACT-G scores (greater than or equal to the median) had significantly higher overall survival (8.94 months vs 10.02 months, respectively) and progression-free survival (4.4 months vs 4.86 months, respectively). Those patients with higher FACT–Physical Well-Being (PWB) scores and FACT–Functional Well-Being (FWB) scores had similarly improved overall survival and progression-free survival. Moreover, when looking at functional status using a traditional ECOG score, they found that among subjects with a performance status of 2 out of 5 (with 2 generally considered the lowest functional group deemed appropriate for most chemotherapies), those with higher FACT-PWB scores, had a 48% reduction in risk of death and better overall survival by nearly 3 months. Similarly, Ashing and colleagues[14] found that patients with a FACT–Cervical Cancer-Specific (CX) score greater than or equal to the median score had significantly improved overall survival. Furthermore, von Gruenigen and colleauges[15] examined the FACT-PWB scores of subjects with ovarian cancer and found that those in the lowest quartile (25%) of scores had decreased overall survival compared with those in the highest quartile, and that for every mean point increase in the FACT-PWB score, death rates decreased by 20%.

Cella and colleagues[16] used several renal cell cancer QOL scores to go a step further and create a tool that predicted overall survival from baseline QOL scores in patients receiving sunitinib and interferon alpha. Although this tool included a few psychosocial questions (eg, it addressed level of worry and how bothered a patient was by side effects), most questions addressed physical symptoms, such as fatigue, pain, weight loss, cough, fevers, and appetite. The investigators found this tool predicted median overall survival based on the HRQOL score. For instance, a score of 20 (with 0 equivalent to the most symptoms and 60 equivalent to no symptoms) predicted an estimated median survival of 29 weeks, whereas a score of 50 predicted to an estimated median survival of 142 weeks.

Though studies suggest the composite scores of HRQOL and physical symptoms are significant to patient outcomes, including survival, individual physical symptoms have also been examined, with fatigue being the most common. In a study by Wang and colleagues,[17] moderate to severe fatigue was reported in 45% of subjects with cancer who were undergoing treatment and 29% of survivors. In a study by Kreissl and colleagues,[18] 27% to 31% of subjects with Hodgkin lymphoma reported fatigue even 5 years after the end of treatment. Fatigue is particularly relevant because data continue to emerge showing that fatigue alone affects survival. For instance, in a study comparing subjects with esophageal cancer who reported normal energy levels (267 subjects, 41%) versus decreased energy levels (392 subjects, 59%), the subjects with normal energy levels had a significantly improved 5-year survival of 37% compared with 28% of those with decreased energy levels (HR 0.74, P = .006).[19] Peters and colleagues[20] examined fatigue in recurrent high-grade glioma subjects and found that increased fatigue predicted poorer survival independent of age, KPS, tumor grade, and number of prior progressions, although the composite scores of FACT-G and FACT-Brain (BR) Tumor specific scores were not independent prognosis factors.

PSYCHOSOCIAL BURDEN

Although the physical symptoms of cancer and treatment can be devastating, so can the psychosocial aspects of cancer. The psychosocial aspects of cancer encompass multiple aspects of distress, including mental health, social functioning, interpersonal relationships, cognitive function, and role functioning. It is estimated that up to 75% of patients with a cancer diagnosis experience psychological distress.[21] With such high prevalence, the impact of these symptoms can be profound.

Two studies highlight the influence of the global psychosocial component of cancer care on outcomes. Groenvold and colleagues[22] examined psychological distress, as well as fatigue, in more than 1500 subjects with breast cancer. Using several surveys to evaluate psychological distress, the investigators initially surveyed subjects at 2 months after primary surgical intervention with a mean follow-up of 13 years. Controlling for variables (eg, stage, histopathology), low-level psychological distress (above the median) was associated with longer progression-free survival and overall survival. The same associations were also found with low fatigue levels. A low level of anxiety was significantly associated with longer progression-free survival but not overall survival. Notably, there have been prior studies of subjects with breast cancer that have not found these same associations.[23,24] However, as Groenvold and colleagues[22] point out, these were generally much smaller studies or controlled for fewer variables. Another study of self-reported HRQOL in 254 subjects with advanced gastric cancer found that social functioning was an independent significant prognostic factor for overall survival, along with more traditional prognostic factors, such as age, bone metastasis, and hemoglobin level.[25]

Although there are multiple, deeply researched components of the psychosocial impact of cancer, depression is the focus going forward in this section given the extent of research on this topic. Several studies have shown associations between depression and mortality or

survival outcomes in malignancy, including breast cancer,[26] head and neck cancer,[27] lung cancer,[28] pancreatic cancer,[29] and prostate cancer,[30] to name a few.

Several large reviews of depression encompassing multiple cancer diagnoses have demonstrated a relationship between depression and survival outcomes. In 2010, Pinquart and Duberstein[31] completed a meta-analysis of depression and cancer mortality. They identified 76 prospective studies spanning multiple cancer diagnoses, including breast, leukemia, lymphoma, lung, colon, and pancreas. They found that after controlling for confounding variables (eg, more advanced disease), associations between depression and higher mortality persisted. Irwin and colleagues[32] reviewed the literature regarding depression and insomnia and found that the prevalence of depression in patients with cancer is likely between 10% and 20% compared with the national average of 5%. They also found that depression triples the risk for nonadherence to medications and significantly increases mortality (19%–39% higher risk). Finally, a third review by Satin and colleagues,[33] which also encompassed several different cancer diagnoses, found that mortality rates were 25% higher in patients with cancer who have depressive symptoms and up to 39% higher in patients diagnosed with minor or major depression. Thus, mounting evidence from several reviews and several individual trials have demonstrated an association between depression and mortality in patients with cancer, independent of other factors, which leads to the argument that the psychosocial issues of patients with cancer need to be addressed as a regular part of overall care.

FINANCIAL BURDEN

Although traditionally not included in HRQOL, financial toxicity, defined as the financial burden and associated distress that result from a cancer diagnosis and/or treatment,[34] is recognized as another key facet of cancer care and patient outcomes. Approximately 42% of patients experience considerable financial burden secondary to cancer and its treatment.[35] For instance, patients with cancer in Washington State are 2.7 times more likely to declare bankruptcy than those without cancer.[36] Financial toxicity affects patients with cancer, families, and outcomes in several ways. First, adherence to treatment can be significantly decreased by financial burden. Dusetzina and colleagues[37] found that subjects with chromic myeloid leukemia who had higher copayments were 42% more likely to be nonadherent to tyrosine kinase therapy. Further, in a cross-sectional study of financial toxicity, subjects reported that financial distress was a greater burden than physical, social, family, and emotional distress.[38]

Given the impact of physical and psychosocial factors on mortality and survival (see previous discussion), it is not surprising that financial toxicity has also been associated with worsened mortality. Perrone and colleagues[39] examined financial toxicity in relation to QOL and increased risk of death at baseline and during treatment from 16 prospective trials in breast, lung, and ovarian cancer. At baseline, 26% of subjects were found to have a financial burden that correlated with worse global QOL but was not associated with increased risk of death. During treatment, however, 22.5% developed financial toxicity and this was associated with increased risk of death (HR 1.20, 95% CI 1.05–1.37, $P = .007$). Furthermore, Ramsey and colleagues,[40] who first showed the increase in bankruptcy risk among patients

with cancer in Washington State, found that patients with cancer who filed for bankruptcy had significantly higher risk for mortality with an adjusted HR of 1.79 (95% CI 1.64–1.96). Despite the limited number of studies available, likely owing to the relative infancy of the field, the financial burden of cancer treatment seems to play a critical role in overall cancer care. This critical aspect of care increasingly needs to be addressed to optimize quality and outcomes.

HOW DO WE INTERVENE?

As previously highlighted, there is a strong body of literature to support the impact of HRQOL, including physical burden, psychosocial burden, and financial burden, on quality and patient outcomes. The next major challenge to address is how oncology providers and health systems can intervene. Although the answer to this question is the subject of ongoing investigation, this section reviews potential strategies that begin to address and mitigate the important issues surrounding HRQOL, as well as highlights specific strategies in relation to the individual symptoms previously highlighted (fatigue and depression), given that these are representative symptoms with abundant data.

The guidelines produced by The National Comprehensive Cancer Network (NCCN) on distress management provide guidance on how to incorporate HRQOL interventions into daily practice. The NCCN recommends screening for distress at every medical visit. When identified, resources should be readily available to help address these concerns, including mental health providers and chaplains. The NCCN provides the Distress Thermometer, a tool for assessment of distress that is used by many institutions. The Distress Thermometer addresses physical symptoms, emotional health, family or interpersonal issues, spiritual concerns, financial distress, and functional concerns.[41] The NCCN also recommends interdisciplinary committees to help develop standards and guidelines for individual institutions.

Recently, Basch and colleagues[42] have shown that symptom assessment and management outside of the usual medical visits is feasible and improves outcomes. In a study of subjects with advanced solid tumor who were undergoing outpatient chemotherapy, subjects were randomized to 2 arms. The first was an intervention arm, which consisted of self-reporting of 12 symptoms via an online tool through tablets or computers. In this arm, reporting of symptoms was encouraged between medical visits, as well as during encounters. The second arm, the control, arm included symptom discussion and management only at visits. HRQOL improved by 34% in the intervention arm versus 18% in the control, or usual care, arm. Furthermore, fewer subjects in the intervention arm had worsened HRQOL (38%) compared with 53% in the usual care arm. The intervention arm also experienced fewer visits to the emergency department, fewer hospitalizations, and tolerated chemotherapy longer than the usual care arm. After a median follow-up of 7 years, median overall survival was 5 months longer in the intervention arm than in the control arm; this finding was statistically significant.[43] This ground-breaking study supports the claim that integrating technology for better symptom monitoring and management may be vital to integrated care, improved QOL, and better outcomes.

After the tools are in place to recognize distress and HRQOL issues, providers should focus on how to address those symptoms. A recurrent theme, particularly regarding the psychosocial component of HRQOL, is coordination and integration of care. Truly integrating psychosocial services into cancer care requires several key components according to Fann and colleagues.[44] These include (1) psychosocial care managers who can serve as links between the services available and primary care providers (eg, shared staff and locations), (2) systemic follow-up of symptoms and adherence to treatment recommendations (eg, using technology assessment tools, similar to methods used to identify and monitor symptoms initially), (3) patient education regarding psychosocial issues and the importance of self-care, (4) brief evidence-based psychosocial treatments that can be executed by care managers under the supervision of specialists (eg, cognitive behavioral therapy), and (5) a management model allowing for stepwise escalation of intervention based on guidelines and response to treatment. Ideally, visits are coordinated and delivered in the same location (eg, the cancer center), though some evidence suggests home-based multidimensional survivorship programs had at least a shortterm benefit in improving global QOL, as well as controlling symptoms such as anxiety, fatigue, and insomnia.[45]

Part of a management model might also incorporate less traditional means of addressing psychosocial issues. Dobos and colleagues[46] integrated a mindfulness program for cancer survivors into cancer care. The investigators showed statistically significant improvement in physical, emotional, cognitive, and social functioning, as well as improvements in symptoms such as fatigue and pain. Of note, this was an intense, 6-hour intervention once a week for 11 weeks, so feasibility of dissemination could be challenging.

For individual symptoms such as fatigue and depression, many of the strategies for improvement in global HRQOL previously outlined are applicable at the individual symptom level, particularly the emphasis on a multipronged and interdisciplinary approach. For instance, the NCCN has published clinical practice guidelines for several individual symptoms, including fatigue. They recommend a multitiered approach that includes education, physical activity (exercise is a NCCN category 1 recommendation due to high level evidence), psychosocial interventions (eg, counseling, cognitive behavioral therapy, journal writing), and pharmacologic treatments (eg, methylphenidate or modafinil, though data are limited and the recommendation is controversial).[47] Highlighting the role of physical activity, Yeo and colleagues[48] designed a randomized prospective trial of an at-home walking program for subjects with pancreas and periampullary cancer after resection. The investigators found that subjects in the intervention group had improved fatigue, pain, physical functioning, and mental health composite scores, though no overall survival benefit was identified.

Guidelines addressing depression in patients with cancer also recommend an integrated approach. For instance, the American Society of Clinical Oncology published guidelines in 2014 that recommend various treatment pathways based on severity of symptoms.[49] These guidelines recommend a range of options from a baseline of supportive care services for all patients regardless of depression or anxiety score to cognitive behavioral therapy, group psychosocial interventions, structured physical activity, and pharmacologic intervention. Of note, pharmacologic interventions, such as selective serotonin reuptake inhibitors, have been

evaluated for use in patients with cancer. Although they certainly have a role for patients with depression regardless of cancer diagnosis, Stockler and colleagues[50] found that, unless subjects met criteria for major depression, treatment with antidepressants did not improve symptoms compared with placebo. Furthermore, Ostuzzi and colleagues[51] performed a Cochrane Database review of antidepressants in patients with cancer and did not find enough evidence to make a general conclusion, which they noted was partly due to few quality studies. Thus, they recommended that the decision to treat with antidepressants be based on each patient's individual situation.

Financial toxicity is another challenging concern that must be addressed. Though certain causes of financial toxicity are beyond the immediate influence of clinicians (eg, insurance design and high drug prices), there are several opportunities for medical professionals to immediately intervene. As noted by Zafar and colleagues,[52] and Goldstein,[53] there are several potential levels of intervention. First, physicians need to inquire about and address affordability at each visit, not unlike regular assessments for other physical or psychosocial symptoms. Integrated and coordinated interventions should then be in place to help connect patients to available financial resources. Second, physicians need to focus on value-based care and be prepared to have frank discussions with patients regarding unnecessary treatments and tests, as well as incorporate cost into the discussion when deciding between equivalent treatments. Finally, long-term solutions need to focus on policy changes that focus on affordable drug pricing and insurance models.

SUMMARY

Evidence continues to accumulate on the importance of HRQOL in all aspects of patient care, including overall survival and other key outcomes. Interventions exist, and continue to evolve, that improve global HRQOL, including physical symptoms, psychosocial symptoms, and financial toxicity. To ensure that patients with cancer receive optimal care and experience the best possible outcomes, these aspects of HRQOL need to be addressed on a regular basis with interdisciplinary and integrated services.

REFERENCES

1. Cella DF. Measuring quality of life in palliative care. Semin Oncol 1995;22(2 Suppl 3):73–81. [PubMed: 7537908]

2. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. US Food and Drug Administration; 2009.

3. Quinten C, et al. Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. Lancet Oncol 2009;10(9):865–71. [PubMed: 19695956]

4. Epplein M, et al. Quality of life after breast cancer diagnosis and survival. J Clin Oncol 2011;29(4): 406–12. [PubMed: 21172892]

5. Osthus AA, et al. Health-related quality of life scores in long-term head and neck cancer survivors predict subsequent survival: a prospective cohort study. Clin Otolaryngol 2011;36(4):361–8. [PubMed: 21624101]

6. McKernan M, et al. The relationship between quality of life (EORTC QLQ-C30) and survival in patients with gastro-oesophageal cancer. Br J Cancer 2008; 98(5):888–93. [PubMed: 18268490]

7. Braun DP, Gupta D, Staren ED. Predicting survival in prostate cancer: the role of quality of life assessment. Support Care Cancer 2012;20(6):1267–74. [PubMed: 21710307]

8. Braun DP, Gupta D, Staren ED. Quality of life assessment as a predictor of survival in non-small cell lung cancer. BMC Cancer 2011;11:353. [PubMed: 21843358]

9. Cella DF, et al. The functional assessment of cancer therapy scale: development and validation of the general measure. J Clin Oncol 1993;11(3):570–9. [PubMed: 8445433]

10. Cella DF, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995;12(3): 199–220. [PubMed: 7655830]

11. Ward WL, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. Qual Life Res 1999;8(3): 181–95. [PubMed: 10472150]

12. Extermann M, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. Cancer 2012;118(13):3377–86. [PubMed: 22072065]

13. Reck M, et al. Baseline quality of life and performance status as prognostic factors in patients with extensive-stage disease small cell lung cancer treated with pemetrexed plus carboplatin vs. etoposide plus carboplatin. Lung Cancer 2012;78(3):276–81. [PubMed: 23043970]

14. Ashing-Giwa KT, Lim JW, Tang J. Surviving cervical cancer: does health-related quality of life influence survival? Gynecol Oncol 2010;118(1):35–42. [PubMed: 20382414]

15. von Gruenigen VE, et al. The association between quality of life domains and overall survival in ovarian cancer patients during adjuvant chemotherapy: a Gynecologic Oncology Group Study. Gynecol Oncol 2012;124(3):379–82. [PubMed: 22119995]

16. Cella D, et al. Baseline quality of life as a prognostic survival tool in patients receiving sunitinib for metastatic renal cell carcinoma. Br J Cancer 2012; 106(4):646–50. [PubMed: 22240794]

17. Wang XS, et al. Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. Cancer 2014;120(3):425–32. [PubMed: 24436136]

18. Kreissl S, et al. Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. Lancet Oncol 2016;17(10):1453–62. [PubMed: 27612583]

19. Stauder MC, et al. Overall survival and self-reported fatigue in patients with esophageal cancer. Support Care Cancer 2013;21(2):511–9. [PubMed: 22842921]

20. Peters KB, et al. Impact of health-related quality of life and fatigue on survival of recurrent high-grade glioma patients. J Neurooncol 2014;120(3):499–506. [PubMed: 25115739]

21. Galway K, et al. Psychosocial interventions to improve quality of life and emotional wellbeing for recently diagnosed cancer patients. Cochrane Database Syst Rev 2012;(11):CD007064. [PubMed: 23152241]

22. Groenvold M, et al. Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. Breast Cancer Res Treat 2007;105(2): 209–19. [PubMed: 17203386]

23. Efficace F, et al. Health-related quality of life parameters as prognostic factors in a nonmetastatic breast cancer population: an international multicenter study. J Clin Oncol 2004;22(16):3381–8. [PubMed: 15310784]

24. Goodwin PJ, et al. Health-related quality of life and psychosocial status in breast cancer prognosis: analysis of multiple variables. J Clin Oncol 2004;22(20): 4184–92. [PubMed: 15483029]

25. Park SH, et al. Self-reported health-related quality of life predicts survival for patients with advanced gastric cancer treated with first-line chemotherapy. Qual Life Res 2008;17(2):207–14. [PubMed: 18224458]

26. Goodwin JS, Zhang DD, Ostir GV. Effect of depression on diagnosis, treatment, and survival of older women with breast cancer. J Am Geriatr Soc 2004;52(1): 106–11. [PubMed: 14687323]

27. Barber B, et al. Depression and survival in patients with head and neck cancer: a systematic review. JAMA Otolaryngol Head Neck Surg 2016;142(3):284–8. [PubMed: 26796781]

28. Sullivan DR, et al. Longitudinal changes in depression symptoms and survival among patients with lung cancer: a national cohort assessment. J Clin Oncol 2016;34(33):3984–91. [PubMed: 27996350]

29. Boyd CA, et al. The effect of depression on stage at diagnosis, treatment, and survival in pancreatic adenocarcinoma. Surgery 2012;152(3):403–13. [PubMed: 22938900]

30. Prasad SM, et al. Effect of depression on diagnosis, treatment, and mortality of men with clinically localized prostate cancer. J Clin Oncol 2014;32(23):2471–8. [PubMed: 25002728]

31. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychol Med 2010;40(11):1797–810. [PubMed: 20085667]

32. Irwin MR. Depression and insomnia in cancer: prevalence, risk factors, and effects on cancer outcomes. Curr Psychiatry Rep 2013;15(11):404. [PubMed: 24078066]

33. Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. Cancer 2009;115(22):5349–61. [PubMed: 19753617]

34. Zafar SY, Abernethy AP. Financial toxicity, part I: a new name for a growing problem. Oncology (Williston Park) 2013;27(2):80–1, 149. [PubMed: 23530397]

35. Zafar SY, et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. Oncologist 2013;18(4):381–90. [PubMed: 23442307]

36. Ramsey S, et al. Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. Health Aff (Millwood) 2013; 32(6):1143–52. [PubMed: 23676531]

37. Dusetzina SB, et al. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 2014;32(4):306–11. [PubMed: 24366936]

38. Delgado-Guay M, et al. Financial distress and its associations with physical and emotional symptoms and quality of life among advanced cancer patients. Oncologist 2015;20(9):1092–8. [PubMed: 26205738]

39. Perrone F, et al. The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy. Ann Oncol 2016;27(12):2224–9. [PubMed: 27789469]

40. Ramsey SD, et al. Financial insolvency as a risk factor for early mortality among patients with cancer. J Clin Oncol 2016;34(9):980–6. [PubMed: 26811521]

41. Frost GW, et al. Use of distress thermometers in an outpatient oncology setting. Health Soc Work 2011;36(4):293–7. [PubMed: 22308881]

42. Basch E, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. J Clin Oncol 2016; 34(6):557–65. [PubMed: 26644527]

43. Basch EM, et al. Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. J Clin Oncol 2017;35(15_suppl):LBA2.

44. Fann JR, Ell K, Sharpe M. Integrating psychosocial care into cancer services. J Clin Oncol 2012;30(11):1178–86. [PubMed: 22412139]

45. Cheng KKF, et al. Home-based multidimensional survivorship programmes for breast cancer survivors. Cochrane Database Syst Rev 2017;(8):CD011152. [PubMed: 28836379]

46. Dobos G, Overhamm T, Büssing A, et al. Integrating mindfulness in supportive cancer care: a cohort study on a mindfulness-based day care clinic for cancer survivors. Support Care Cancer 2015;23(10):2945–55. [PubMed: 25711654]

47. Denlinger CS, et al. Survivorship: fatigue, version 1.2014. J Natl Compr Canc Netw 2014;12(6): 876–87. [PubMed: 24925198]

48. Yeo TP, et al. A progressive postresection walking program significantly improves fatigue and health-related quality of life in pancreas and periampullary cancer patients. J Am Coll Surg 2012;214(4):463–75 [discussion: 475–7]. [PubMed: 22321518]

49. Andersen BL, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol 2014;32(15):1605–19. [PubMed: 24733793]

50. Stockler MR, et al. Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled doubleblind randomised trial. Lancet Oncol 2007;8(7):603–12. [PubMed: 17548243]

51. Ostuzzi G, et al. Antidepressants for the treatment of depression in people with cancer. Cochrane Database Syst Rev 2015;(6):CD011006. [PubMed: 26029972]

52. Zafar SY. Financial toxicity of cancer care: it's time to intervene. J Natl Cancer Inst 2016;108(5) [pii:djv370].

53. Goldstein DA. Financial toxicity in cancer care-Edging toward solutions. Cancer 2017;123(8): 1301–2. [PubMed: 28218808]

KEY POINTS

- Overall health-related quality of life has been associated with risk of mortality and cancer-related outcomes.

- Assessment and intervention of psychosocial and physical symptom burden can improve the experiences of patients with cancer and may improve survival.

- The growing financial burden experienced by patients also requires assessment and intervention, without which outcomes are worsened.