Health-Related Quality of Life Assessment in Breast and Prostate Cancer

Case Study and Commentary, David Osoba, BSc, MD, FRCPC

INSTRUCTIONS
The following article, “Health-Related Quality of Life Assessment in Breast and Prostate Cancer,” is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 67.

OBJECTIVES
After participating in the CME activity, primary care physicians should be able to:
1. Understand the contributions of HRQL assessment to the care of patients with cancer
2. Be able to explain to patients reasons for choosing breast-conserving surgery over modified radical mastectomy as the primary surgery for breast cancer
3. Respond to patients questions and needs related to the effects of chemotherapy toxicity on HRQL
4. Appreciate the value of combined chemotherapy and corticosteroids for improving the HRQL of patients with metastatic hormone-resistant prostate cancer
5. Appreciate the uncertainty that still remains regarding the ability of HRQL data to inform clinical practice

INTRODUCTION
Over the past decade, changes in health-related quality of life (HRQL) have been accepted as important outcomes. HRQL can be defined as the impact of an illness and its treatment on the functional ability and well-being of an individual (or group of individuals) as reported by the individual over time. Unlike health status, which may be assessed in disease-free populations, HRQL is assessed only in populations with disease. HRQL also differs from symptom control in that improvement in symptom control may result in improvement of HRQL, but the absence of symptoms is not synonymous with optimal HRQL. Thus, HRQL encompasses some aspects of health status and symptom control.

HRQL is usually assessed by self-report questionnaires containing a series of questions grouped into domains. At a minimum, HRQL questionnaires assess patients’ physical, emotional, and social functioning, but other domains such as cognitive functioning, somatic complaints (symptoms), and spiritual concerns have been suggested for inclusion in some questionnaires. Assessment of HRQL has become an integral component of many clinical trials, including oncology clinical trials. (See Table for a partial listing of reliable and valid questionnaires used in oncology.) The HRQL data obtained from these studies has improved our understanding of the effects of cancer and its treatment on patients’ ability to function physically, socially, and emotionally. Knowing the HRQL benefits associated with various treatments can be helpful in clinical decision making, particularly when the clinical outcomes of a treatment are similar. This paper provides a review of clinical studies in breast and metastatic prostate cancer that have included HRQL assessment and presents 2 case studies that illustrate the value of HRQL information when treating patients with these types of cancer.

CASE STUDY 1
Initial Presentation
A 39-year-old Caucasian women is referred to a surgeon by her primary care provider after discovering a lump in her left breast on self-examination 1 week ago.

History
The patient has no other complaints and has always been very active and “physically fit.” She is married and has 2 daughters. Three of her 4 siblings are female. There is no history of breast cancer in her family.

Physical Examination
The patient is 5’7” tall and weighs 154 lb. The general physical examination is within normal limits other than for a mass in the upper outer quadrant of the left breast and probable left axillary lymphadenopathy.

Laboratory and Imaging Studies
Results of routine hematologic and biochemistry testing are

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within normal limits. A standard chest radiograph is “suspi-
cious” for left hilar enlargement, but a subsequent comput-
erized tomography (CT) scan is reported as being normal.

The surgeon discusses treatment options with the patient.
She suggests a fine needle biopsy of the mass to be followed
immediately by further surgery if the biopsy is positive for
cancer. She advises that the patient may choose either modi-
fied radical mastectomy (MRM) or breast conserving
surgery (BCS), each followed by adjuvant chemotherapy
and radiation to the chest wall and regional node-bearing
areas.

• What is the effect of type of initial surgery on HRQL?

Effects of Surgery

Current evidence suggests that survival in early-stage inva-
sive cancer is similar after both types of surgery [26]. Thus,
HRQL is a logical criterion to apply in making decisions
about type of therapy. During the past 2 decades, there has
been a shift away from MRM toward BCS. Early studies on
the impact of MRM on HRQL emphasized the effects of
changed body image on sexuality and overall well-being;
many of these studies were anecdotal. More recent meta-
analyses and reviews [27–30] have suggested that BCS is
associated with less distress from altered body image and
perhaps better sexual functioning than is MRM. However,
because these reviews deal with studies in which the
patients were surveyed retrospectively, selection bias cannot
be completely excluded as an explanation of the results.
Selection bias is also possible in single retrospective studies
[31,32]. Also, all these retrospective studies do not reach the
same conclusions. For example, one study [33] suggests that
age may be an important determinant while another [31]
concludes that age was not associated with the observed
changes in HRQL. Nonrandomized studies in which the
HRQL data were gathered prospectively support the con-
clusions of the retrospective studies that BCS was associated
with improved quality of life (QOL), but note that by 1 year
after surgery the deleterious effects of MRM on body image
had disappeared, leaving no differences between the
patients treated with MRM and BCS [34–36]. Pain in the sur-
gically affected area may actually be worse following BCS
and axillary lymphadenectomy than after MRM [37]. One
randomized controlled trial [38] concluded that BCS was
associated with greater maintenance of body image and
higher satisfaction than was MRM; no other differences were
found in HRQL parameters. However, completion rates of
the HRQL questionnaire were low in this study, and the
effect of possible selection bias must be considered. In sum-
mary, despite the lack of unflawed randomized controlled
trials, most of the available evidence suggests that BCS is the
treatment of choice for early stage breast cancer because it is
associated with better HRQL over the short to mid term. One
year after surgery, the HRQL effects are probably similar
with both types of surgery, possibly because of adaptation to
the effects of MRM.

It should be noted that although lymphedema occurs
infrequently (10%), it is a significant complication after axil-
lar extirpation and is associated with adverse HRQL effects
[39,40].

Recently it has been suggested that reconstructive breast
surgery should be offered to women immediately after the
initial surgery, particularly if they have had neoadjuvant
(preoperative) chemotherapy, rather than waiting for 2 years
as is often advocated [41]. This recommendation is made on
the grounds that breast reconstruction would likely be asso-
ciated with improvements in HRQL. However, HRQL data
obtained directly from women undergoing reconstructive
surgery after preoperative chemotherapy are not provided
to support this recommendation.

Surgical Treatment

The results from needle biopsy are positive. The
patient feels that having BCS would leave doubt in
her mind about whether “all the cancer had been removed.”
She undergoes a left-sided MRM. The left breast contains a mass measuring 1.5 cm × 1.5 cm, and 6 of 14 left axillary nodes are involved with an invasive (infiltrating) ductal carcinoma. Following surgery, the patient is evaluated for chemotherapy and radiation therapy at a comprehensive cancer center. There are no abnormal findings on physical examination except for evidence of the recent surgery. Her estrogen receptor status is positive. Bone and liver scans are within normal limits. She is treated with a course of adjuvant chemotherapy, consisting of 6 cycles of cyclophosphamide, doxorubicin, and 5-fluorouracil, followed by radiation therapy to the chest wall and axilla.

**Effects of Chemotherapy**

Adjuvant chemotherapy and chemoendocrine therapy of node-positive breast cancer have been reported to result in improvements in HRQL over baseline measures despite initial minor, transient adverse effects [42]. This conclusion was based mainly on improved scores on the Perceived Adjustment to Chronic Illness Scale (PACIS) [43], but other parameters such as physical well being, mood, and appetite were also found to be improved. Improvement in HRQL was delayed in those receiving longer initial chemotherapy due to the longer duration of side effects. However, the deleterious effects as measured in this study were transient. Some long-term side effects (eg, decreased cognitive functioning and fatigue) were not measured in this study, perhaps because they were not anticipated at the time the study was designed.

An Eastern Cooperative Oncology Group (ECOG) study involving patients with hormone-receptor negative, node-positive breast cancer evaluated whether a dose-intensive adjuvant chemotherapy regimen given for 16 weeks would have an adverse effect on HRQL that was not balanced by improvements in disease control or survival [44,45]. Patients were randomized to a standard regimen of cyclophosphamide, doxorubicin, and 5-fluorouracil or an intensive 16-week multidrug regimen. HRQL was assessed using the self-administered Breast Cancer Questionnaire (BCQ) prior to, during, and 4 months after therapy. BCQ scores worsened more during the intensive regimen than during the standard regimen; however, by 4 months post-treatment, intensive regimen scores were higher than at pretreatment and scores in the 2 arms were equal. Patients treated with the intensive regimen averaged 1.4 fewer months of treatment with toxicity and 4 more months without symptoms; however, they experienced only 0.7 fewer months postrecurrence (ie, time from first relapse to death) than patients who received the standard regimen. These results suggest a small gain in HRQL for the intensive 16-week regimen, but definite conclusions could not be made because of a relatively short follow-up time (mean, 4 years).

**Side Effects of Chemotherapy**

The side effects of chemotherapy depend on the antineoplastic agents used but generally include anorexia, emesis, hair loss, fatigue, and myelosuppression. All of these effects are thought to be transient and reversible. Until recently, however, the impact of these and other side effects on HRQL has not been well described.

While the studies discussed above [42–45] claimed little, if any harm, to HRQL for patients treated with adjuvant chemotherapy, other studies have described troubling side effects of chemotherapy, including decreased cognitive functioning (sometimes called “chemo fog”) [46]. When assessed by the High Sensitivity Cognitive Screen and Profile Mood Status (POMS), a group of 31 breast cancer patients receiving chemotherapy and a group of 40 patients who had completed adjuvant chemotherapy 2 years earlier showed moderate or severe cognitive impairment compared with a control group of 36 healthy women (P = 0.002) [46]. These differences did not seem to be associated with significant differences in mood disturbance. This study confirms the findings of earlier studies [47,48].

Studies indicate that fatigue is a major side effect of adjuvant chemotherapy for breast cancer [49–51] and may become a long-term side effect [52]. Fatigue may persist for several years after adjuvant chemotherapy [53,54]. About one third of breast cancer survivors report severe fatigue that is associated with higher levels of depression, pain, and sleep disturbance [53]. In the Bower et al study, depression and pain were the strongest predictors of fatigue. However, it is important to note that fatigue is one of the most common side effects of chemotherapy [53,56–61] as well as the most common symptom in advanced cancer. It is important to distinguish between the 2 etiologies.

Fatigue and decreased cognitive functioning are troubling side effects, particularly since they seem to be long term in duration. Because many trials are using chemotherapy before primary surgery [62], the number of women at risk for these HRQL impairments will increase substantially. Definitive data are needed to better understand the trade-offs that patients with breast cancer will have to make when considering treatment methods. In the meantime, it may be concluded that the benefits of chemotherapy outweigh the short-term side effects, and while longer-term side effects are cause for concern, there is no alternative therapeutic maneuver currently available to replace this mode of therapy.
**HRQL ASSESSMENT IN CANCER**

**Patient Follow-up**

As expected, the patient complains of fatigue while receiving chemotherapy and radiation therapy, but 1 year later she seems to have recovered fully from treatment. Tests of cognitive function are not done. She has neither nausea nor vomiting during the chemotherapy.

Four years later during a visit to her primary care physician, the patient reports that she experienced unusual shortness of breath while hiking recently. She subsequently noticed shortness of breath while climbing stairs, and 2 weeks ago felt “slightly” breathless while at rest. She is not short of breath while sleeping. Two weeks ago she also noticed a “twinge” in her mid-lower back while playing with her 3-year-old granddaughter. The pain has steadily increased to the point where she is aware of it most of the time and takes acetaminophen with codeine at night to “get comfortable.” Her last menstrual period began 2 weeks ago.

Her hemoglobin is 10.5 g/100 mL with microcytic, normochromic red blood cells. The white blood cell count and differential are within normal limits. A radionuclide bone scan shows increased uptake in the T12-L1 region as well as in the third and fourth right ribs anterolaterally. There is questionable increased uptake in the left upper femur. A standard chest radiograph shows an enlarged left hilum and confirms a left pleural effusion. A CT scan of the upper abdomen shows at least 3 space-occupying lesions in the right lobe of the liver, the largest of which is 2 × 2 cm. However, liver function tests are within normal limits.

**Diagnosis and Treatment**

The physician makes a diagnosis of invasive (infiltrating) ductal carcinoma with metastases to left axillary nodes (remote) and to left hilar nodes, liver, and the axial skeleton. She is given a systemic anthracycline-containing chemotherapy regimen every 3 weeks for 6 cycles. Ondansetron and dexamethasone are given to control nausea and vomiting. Pleurocentesis and pleurodesis are performed.

- Does administration schedule of the chemotherapy have an effect on HRQL?

**Chemotherapy Scheduling**

One of the earliest studies on HRQL involving a large number of patients with metastatic breast cancer considered whether continuous cycles of chemotherapy would be more deleterious to HRQL than the same chemotherapy given for fewer cycles and then interrupted until further chemotherapy was required [63]. It was expected that giving continuing cycles without a rest period would result in poorer HRQL because of the greater toxicity experienced by the patients. However, the results were contrary to these expectations. HRQL was actually better in the patients who received chemotherapy continuously rather than intermittently. The progression-free interval and survival were also better in the continuous group [64]. These results indicate that a chemotherapy regimen effective in producing tumor regression and improved survival is associated with improvements in HRQL. On the other hand, chemotherapy that is ineffective in reducing tumor burden is unlikely to be associated with improved quality of life. Nonetheless, this assumption must be proven rather than accepted as fact.

It must not be concluded that more chemotherapy is always better chemotherapy for HRQL. Several studies in a variety of cancers, including breast cancer, have shown that very aggressive, dose-intensive chemotherapy may be deleterious to HRQL [65,66]. Deleterious effects also may be exaggerated if chemotherapy is followed within a short interval by radiation therapy [67]. In some advanced cancers, less intensive chemotherapy regimens may actually be as effective as standard regimens [68,69]. However, a recent study in small-cell lung cancer has demonstrated that the intensity of the chemotherapy regimen could be increased by 34% over a standard regimen with equal palliation of symptoms and no significant difference in HRQL [70].

- What is the role of antiemetics in preventing deterioration of HRQL?

**Antiemetic Therapy**

Most of the chemotherapy regimens will contain moderately to highly emetic cytotoxic drugs (cyclophosphamide, doxorubicin, taxanes, or platinum compounds). Postchemotherapy nausea and vomiting disrupt HRQL, with deterioration in physical, cognitive, and social functioning and worsening of fatigue, sleep disruption, appetite, and global quality of life [71–74]. Patients who have nausea without vomiting experience deterioration in HRQL to nearly the same extent as do those with both nausea and vomiting. One or 2 episodes of vomiting are nearly as deleterious to HRQL as more than 2 episodes. Patients with neither nausea nor vomiting still have worsened physical and social functioning, fatigue, and insomnia compared with pretreatment [73]. Thus, the occurrence of postchemotherapy nausea and vomiting does not completely explain worsening of HRQL, and other explanations, probably attributable directly to the chemotherapy, need to be found.

Physicians who treat breast cancer must be thoroughly familiar with the proper use of antiemetics. Premedication with a 5-HT3 receptor antagonist and a corticosteroid are
recommended to prevent post-treatment nausea and vomiting from chemotherapy agents [75]. Recommendations for the use of antiemetics for postchemotherapy and postradiation therapy nausea and vomiting are available [75,76]. The goal of antiemetic therapy should be complete prevention of nausea and vomiting.

• What are additional approaches to treatment in advanced disease, and how do they affect HRQL?

Bisphosphonates

Single bone metastases that are painful or that may lead to imminent fractures are usually best treated with radiation therapy. However, if multiple bone metastases are present or new metastatic sites appear frequently, systemic therapy consisting of a combination of chemoendocrine therapy and bisphosphonates offers the best prospect for reducing the frequency of skeletal events and the severity of pain [77–79]. The results from several pooled studies of clodronate and pamidronate favor these agents over placebo or control treatment when used concomitantly with first-line chemotherapy or hormones [80–86].

Only 3 studies assessed aspects of HRQL in patients with breast cancer who were treated with bisphosphonates [80–82]. One of them reported less mobility impairment, one reported that ECOG performance scores declined less with intravenous pamidronate than with placebo, and one reported no HRQL benefit. However, these studies did not employ comprehensive HRQL instruments but instead assessed only physical aspects of HRQL. Thus, the effect of bisphosphonate treatment on HRQL is still not completely known. However, the American Society for Clinical Oncology guidelines [77] recommend intravenous pamidronate in patients who have pain caused by osteolytic metastases and are receiving concurrent chemotherapy or hormones [80–86].

Treatment of Anemia, Anorexia, and Weight Loss

Anemia is a common complication of metastatic breast cancer. Epoetin alpha given concurrently with myelosuppressive chemotherapy has been shown to increase hemoglobin levels in patients with a variety of cancers [87–91]. Increases in hemoglobin levels are associated with improvement in activity and energy level and overall quality of life [87–89,92]. These positive results need to be confirmed in a large, prospectively randomized controlled trial before routine administration of epoetin alpha during chemotherapy can be recommended.

Anorexia and weight loss occur frequently in women with widely metastatic breast cancer. Although there seems little doubt that megestrol acetate produces weight gain without effects on tumor status in nonhormone responsive tumors, whether there are associated gains in HRQL remains controversial [93–97]. Three large randomized studies (including 599 patients) comparing megestrol with placebo have shown no differences in HRQL, other than improvement of appetite [93,94,97], while a smaller study of 84 patients showed improvement in appetite, activity level, and well-being in the megestrol acetate group compared with the placebo group [96].

The value of megestrol acetate for symptom control and HRQL benefit in metastatic breast cancer is difficult to evaluate because of the possibility of both tumor effects and symptomatic benefits. About 25% to 30% of women will have a tumor response during treatment with megestrol acetate, and this in itself may be associated with HRQL improvement [98–100].

Biologic Therapy

The effectiveness of treatment with trastuzumab (Herceptin, an anti-HER2/Neu antibody) in a subset of patients with advanced breast cancer has been established [101–103]. Effects on HRQL show that the addition of trastuzumab to chemotherapeutic regimens has not resulted in decreased HRQL scores [104]. Development of cardiomyopathy during trastuzumab therapy is a concern; however, since the number of patients developing cardiomyopathy is small, it has not been possible to assess HRQL adequately in this subgroup.

• Is there a role for group psychotherapy in the management of advanced breast cancer?

Group Psychotherapy

Until recently, there has been a paucity of empirical information about the effects of group psychotherapy on HRQL [105]. The main focus in empirical studies has been on mood (particularly, anxiety and depression) and coping skills [106–111]. In most studies, the participants have had a heterogeneous mix of cancers, including breast cancer, while there have been few cohorts consisting solely of breast cancer patients [108,109]. In general, these studies can be interpreted as showing benefits of group therapy, such as improvement in coping and less anxiety, tension, depression, and fatigue. Some studies have shown improved vigor and fewer phobias. One study has claimed improved survival in a group of breast cancer patients receiving group therapy [109], while others have found no differences in survival [107,110]. Because very few of these studies have been randomized controlled trials, the possibility of selection bias is strong.
Clinical Course

After completing the chemotherapy regimen for metastatic disease, the patient experiences complete symptomatic improvement lasting for 1 year. With subsequent relapse of the metastatic disease in her bones, she is treated with bisphosphates and tamoxifen, but has only a modest response in symptoms. She dies 6 months later.

CASE STUDY 2
Initial Presentation

A 72-year-old Caucasian man presents with lower back pain of 4 weeks’ duration.

Present History

About 4 weeks ago, the patient noticed the gradual onset of pain in his lower back and right sacroiliac region, associated initially only with activity. The pain is made worse on movement or if he sits for a “long” period of time. The pain wakes him at night, and he is unable to find a comfortable position for sleeping. For the past 2 weeks, he has taken about 4 tablets daily of an analgesic preparation containing acetaminophen and codeine. He experiences only 1 to 2 hours of pain relief after taking this medication.

Past History

Six years ago, the patient underwent a radical prostatectomy for stage II, poorly differentiated adenocarcinoma of the prostate (Gleeson score of 8). Prostate-specific antigen (PSA) levels were within normal limits after surgery, and no radiation therapy or hormonal therapy was given. Three years ago, he presented with lower back pain, and a bone scan revealed increased radionuclide uptake in several areas of the skeleton including the right sacroiliac region. PSA was elevated at 86 ng/mL. He was offered orchiectomy, which he refused, and was instead treated with a luteinizing-hormone releasing hormone (LHRH) agonist. His symptoms disappeared and the PSA levels decreased to 10 ng/mL. He remained asymptomatic for 18 months, but subsequently PSA monitoring again showed an increase in PSA and he had a return of pain. A course of flutamide resulted in some improvement in pain, but the patient stopped taking this medication 3 months prior to his present visit because of side effects (lethargy, impotence).

Physical and Laboratory Examination

The patient is pale and appears chronically ill. There is tenderness to palpation in the right sacroiliac region. He has limited right hip flexion because of pain. A radionuclide bone scan reveals areas of increased uptake in the region of the right sacroiliac joint, in the neck of the left femur, and in several ribs. His hemoglobin is 12.5 g/100 mL, and the white blood cell count, urinalysis, and serum creatinine are normal.

• What are treatment considerations for metastatic prostate cancer?

The mainstay of treatment for metastatic prostate cancer is androgen suppression, either by castration or chemical suppression. Like the patient in the case presentation, some men prefer to be treated by drugs rather than by castration. While orchiectomy is perceived as having a deleterious effect on HRQL [112,113] it seems to have fewer effects than maximum androgen blockade in some studies [114]; in other studies the 2 approaches are perceived as being similar [115]. Little is known about the psychological effects of surgical castration that influence men to decline surgery. There is no difference in time to progression or in survival between these treatment options [116].

• How does androgen blockade affect HRQL?

Androgen Blockade

In a review of 27 phase III clinical trials that used various combinations of androgen deprivation for metastatic prostate cancer, only 3 studies showed a statistically significant benefit for complete androgen blockade [117]. While toxicity and HRQL issues have not been widely investigated in a prospective fashion, the available data suggest a higher toxicity rate and poorer HRQL in men with complete androgen blockade. The overall data do not support the routine use of antiandrogens in combination with medical or surgical castration as a first-line hormonal therapy for metastatic prostate cancer. However, in a study of bicalutamide versus surgical castration, bicalutamide was favored in 8 out of 9 HRQL dimensions, with statistically significant differences in sexual interest and physical capacity [116]. In a nonrandomized study, a group of 79 asymptomatic men with nonmetastatic prostate cancer who chose to be treated by androgen deprivation therapy reported more fatigue, loss of energy, emotional distress, and lower overall HRQL than did 65 patients who refused androgen deprivation [118]. Combinations of androgen deprivation therapy (orchiectomy, leuprolide, or leuprolide plus flutamide) had a greater adverse effect on HRQL than did monotherapy. In a study that compared surgical castration with combined androgen blockade (leuprolide and flutamide), there were no observed differences between the 2 treatment groups in any prostate-targeted or general HRQL domains [115]. Thus, the data between studies are somewhat inconsistent, perhaps as a result of the patient samples studied or differences in the ability of different HRQL instruments to detect changes. However, treatment with a combination of an
LHRH agonist and flutamide may be preferable to having disease progression [119]. In this study, men with hormone-sensitive cancer had significantly less pain, more vitality, more social interactions, and better health than did patients with hormone-resistant disease. HRQL reported by men in remission receiving an LHRH agonist was indistinguishable from a matched population without prostate cancer. The benefit was independent of any possible improvement in longevity.

- How is HRQL affected by treatment for metastatic hormone-resistant prostate cancer?

**Strontium-89 and Bisphosphonates**

Studies of Sr-89 with or without local radiation therapy and of bisphosphonates have focused primarily on control of bone pain. There are several phase II studies that support the use of Sr-89 plus or minus local radiation therapy [120] and of bisphosphonates in advanced prostate cancer [121]. Unfortunately, there are fewer phase III studies and fewer yet that include HRQL outcomes in addition to pain control.

Compared with placebo, Sr-89 has not decreased pain at index sites nor increased survival but has been associated with a statistically significant delay in the appearance of pain at new sites, a reduction in analgesic intake, and an improvement in physical activity [122]. It should be noted that in this study, HRQL was measured with a linear analog self-assessment scale that had not been previously validated in this population. A similar study used physician assessment rather than self-assessment and concluded that although pain relief was achieved there were no differences in the duration of pain relief between patients given Sr-89 plus radiation therapy and those not given this treatment [123]. Fewer new pain sites developed in those treated by Sr-89 and local radiation.

The use of long-term bisphosphonates has not been adequately studied in hormone-resistant prostate cancer. Two phase III studies did not show significant differences in pain control between either oral clodronate or etidronate and placebo; neither of these studies included HRQL assessment [124–126].

**Chemotherapy and Corticosteroids**

Chemotherapy alone has not been effective in prolonging survival [127] in hormone-resistant prostate cancer. Studies of pain palliation and of HRQL show only minimal promise for chemotherapy alone [128,129] or corticosteroids (prednisone) alone [130]. Combinations of corticosteroids (prednisone or hydrocortisone) plus chemotherapy with mitoxantrone [131–133] are much more likely to result in pain control and HRQL benefits. In a randomized controlled trial that compared prednisone to mitoxantrone plus prednisone in 161 men, pain reduction without an increase in analgesic intake was the primary endpoint, while HRQL endpoints were secondary [132]. Differences in survival were not expected and were not found. However, pain reduction without an increase in analgesic intake occurred in 29% of the mitoxantrone/prednisone group compared with 12% of the prednisone group ($P = 0.01$). The mean duration of pain reduction was 43 weeks in the mitoxantrone/prednisone group versus 18 weeks in the prednisone group ($P = < 0.0001$). Furthermore, men taking the combined therapy reported statistically significant improvement in 13 of 22 HRQL domains, in addition to pain improvement, after 4 completed cycles of therapy (12 weeks); men taking prednisone alone reported improvement only in pain [134]. HRQL improvements lasted longer in those who received the combined therapy ($P = 0.04–0.05$). Men whose pain failed to respond to prednisone alone after 6 weeks were eligible to have mitoxantrone added to the prednisone. After addition of mitoxantrone, improvement was noted in 6 of the 22 HRQL domains, suggesting that mitoxantrone may have an independent effect on HRQL. The only deleterious side effect attributable to mitoxantrone was hair loss.

In a similar study, 242 men with hormone-resistant prostate cancer were randomized to receive either hydrocortisone or hydrocortisone plus mitoxantrone [133]. This study was designed to demonstrate an advantage of the combined therapy on survival, but HRQL parameters were also assessed. The HRQL instruments used were different and completion rates were lower than those in the Tannock et al study [132]. However, improvement in pain was demonstrated to be more favorable in the combined therapy arm than in the hydrocortisone arm. No differences in survival were demonstrated.

It can be concluded that both of these randomized controlled trials demonstrate the superiority of mitoxantrone plus a corticosteroid over a corticosteroid alone in providing better pain control and other HRQL benefits.

**Treatment and Clinical Course**

The patient has metastatic hormone-resistant prostate cancer and is treated with a regimen containing oral prednisone and intravenous mitoxantrone. He becomes asymptomatic within 8 weeks of starting chemotherapy. A total of 6 cycles are given. He remains asymptomatic for 4 months after the completion of chemotherapy, but then the pain in the bony metastatic sites returns. He is treated with analgesics with moderately good control of his pain. He dies in a palliative care unit 3 months later.

- How should HRQL assessment be used in routine clinical practice?
We need to be cautious about using HRQL measurement in routine, day-to-day clinical practice. Ideally, all patients presenting to a practitioner’s office, a clinic, or a hospital should be eligible for HRQL assessment and should be assessed longitudinally throughout the course of their illness. However, the instruments in use today were designed for grouping the data from individuals rather than for use over time in a single individual. (See Figure for an example of a trial-specific questionnaire.) The required psychometric properties of instruments for grouped data are less rigorous than those for individual data (e.g., Cronbach’s alpha of > 0.7 is acceptable for grouped data, but an alpha of > 0.9 is preferable for individual data) [135]. The scales in many instruments in current use do not meet the requirement for individuals. The development of individualized questionnaires based on item-response theory [136] will likely overcome this difficulty.

Despite the need for more accurate instruments, the results of randomized, controlled clinical trials obtained with current instruments can be used in routine practice. For example, an understanding of the effects of the disease and its treatment on HRQL can be used to inform a patient of the likelihood of the occurrence of a given result. Referring to the case presentations, the woman with breast cancer could have been informed that BCS is associated with fewer problems with body image and sexual functioning than is MRM, but if she did choose the latter surgical procedure she would likely be able to adapt to the changes. During the course of chemotherapy, she would likely experience a temporary decrease in her ability to function in several HRQL domains, but the long-term benefit would be improved functioning despite underlying fatigue. Furthermore, chemotherapy adequate to produce tumor responses should probably be the goal of chemotherapy for metastatic disease. Until further studies are completed, it would be difficult to give her accurate information about the exact effects of chemotherapy on cognitive functioning. The man with prostate cancer could have been advised that chemotherapy with mitoxantrone and prednisone would likely have a beneficial effect on pain and on other HRQL domains and that the only significant side effect would be hair loss.

**Figure.** Quality of Life Module-Prostate 14 (version 2.0). The QLM-P14 (version 1.0 [134]) was designed as a trial-specific, disease-specific questionnaire to be used in conjunction with a condition-specific questionnaire, such as the QLQ-C30 or FACT-G questionnaires. Neither version is intended for individual use in patients in day-to-day clinical practice. In this version, the items are grouped into 4 domains (pain impact, 1–5; drowsiness, 8–10; pain relief, 11, 12; and dysuria/nocturia/sleep, 7, 13, 14) and 1 single item (hair loss, 6).
An unexpected result from HRQL measurement in cancer has been the discovery that the scores in some HRQL domains have given predictive and prognostic information that was hitherto unknown or that was superior to other known prognostic factors. For example, patients with low social functioning scores before their first cycle of chemotherapy were more likely to suffer from postchemotherapy nausea and vomiting than were patients with higher social functioning scores [137]. In metastatic breast cancer [64], malignant melanoma [138], and colorectal cancer [139], HRQL scores were more accurate in predicting survival than were physical performance status scores (eg, Karnofsky Performance Score, ECOG performance status, WHO performance status). Other studies demonstrating the prognostic value of HRQL information have been reported [140–144].

CONCLUSION

This review of HRQL in metastatic breast and prostate cancer is based mainly on the results of randomized controlled trials. Results from an adequately powered single trial or results reproduced in multiple trials give the most reliable evidence (Level I) for the efficacy of therapy. The available evidence strongly supports the view that HRQL assessment is an informative component of clinical trials. However, the generalizability of results from clinical trials in which the eligible sample is well defined but not necessarily representative of the entire patient population must be viewed with some caution when applying the results to all patients. Similarly, HRQL results should be taken as being representative only of the sample of patients that were studied and are not necessarily generalizable to all patients with that cancer.

Another issue has to do with the meaningfulness of changes in HRQL scores over time. If the sample size is large, statistically significant changes may be found (ie, P values of < 0.05) even when differences in numerical scores are small (eg, 5 on a 0-to-100 scale) because tests of the null hypothesis are highly dependent on sample size. It has been suggested based on empirical data derived from patients with cancer that changes of 10 or more on a 0-to-100 scale are meaningful since patients can easily distinguish this amount of change as being a “moderate change” [145]. However, more work is required in this area. In particular, it is necessary to define what constitutes meaningful change to various users of HRQL information (ie, patients, physicians, health care professionals, policy makers) since it is likely that the numerical value denoting meaningful change will vary among users.

Investigators have initiated intense research efforts to resolve these difficulties. Thus, the future for HRQL research and clinical application is optimistic. Since the ultimate goal of all health care is to preserve or restore HRQL, assessment of HRQL will become an integral part of health care in the future.

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EVALUATION FORM: Health-Related Quality of Life Assessment in Breast and Prostate Cancer

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Part 1. Please respond to each statement.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I was provided with new information pertinent to my practice</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>I reaffirmed a specific skill or knowledge.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>This article will help with clinical decision making.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Relevant clinical outcomes are addressed.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>The case is communicated in a manner that kept my interest.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>The case presentation is realistic and effective.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>I could easily interpret the tables and figures.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>My attitude about this topic changed in some way.</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Additional comments: ______________________________________________________________________________________

__________________________________________________________________________________________________________

Part 2. Please complete the following sentence.
As a result of reading this case study, I . . .
☐ see no need to change my practice.
☐ will seek more information before modifying my practice.
☐ intend to change the following aspect(s) of my practice: (Briefly describe)

__________________________________________________________________________________________________________

Signature: ______________________ Date: ______________________

Part 4. Identifying information: Please PRINT legibly or type the following:
Name: ______________________ Fax number: ______________________
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