Chapter 16
Living with Metastatic Breast Cancer

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Abstract Although prevalence estimates are imprecise, growing numbers of women in the United States are living longer with metastatic breast cancer, attributable at least in part to the availability of effective targeted therapies. Women living with metastatic disease are understudied, however, and substantial heterogeneity exists in both the clinical characteristics of metastatic tumors and the physical and psychological experience of patients living with the disease. Survivorship issues are complex for patients who are living with metastatic disease over extended periods of time, from years to decades. Newly diagnosed patients with stage IV disease are confronting cancer for the first time, while others have metastatic disease as a result of breast cancer recurrence. Many patients are able to live for years on stable medical regimens, and yet others live with a moving target of aggressive disease with arduous treatments and uneven response. The psychological common denominator is the experience of profound life threat and the accompanying uncertainty, for both the affected woman and her loved ones. Maintaining life balance in the face of metastatic disease, as well as managing pain, fatigue, and other physical and psychological symptoms are major challenges. Increasingly, the clinical approach to metastatic disease reflects the consensus that palliative and supportive care are essential from the point of diagnosis. To remedy the paucity of systematic research on women living with metastatic breast cancer for extended periods, we offer directions for research to understand the experience of metastatic breast cancer and to provide evidence-based inter-professional care.

Keywords Metastatic breast cancer • Advanced cancer • Psychological distress • Quality of life

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Introduction

With all of the attention given to early breast cancer detection and the highly favorable outcomes for so many breast cancer patients (Desantis et al. 2014), the small number of women with stage IV disease at diagnosis or who are living for extended periods of time with metastatic disease as a result of breast cancer recurrence are relatively neglected. Now, growing numbers of women and men live for extended periods of time with metastatic disease, some with long durable remissions and others moving from one treatment to the next. This change is attributable to the increased numbers of targeted therapies, especially for hormone sensitive and HER-2 positive disease. Some patients, particularly those with stage IV disease at diagnosis, may enjoy complete remissions or long-lasting control of their disease for extended periods. Others, who experience recurrence of breast cancer after an initial disease-free interval, usually have a more varied course both physically and emotionally. In this chapter, we address the prevalence and clinical heterogeneity of metastatic breast cancer, the physical and psychological consequences of long-term cancer-directed therapy, the experience of women living with metastatic disease, ideally how care should be delivered to these survivors, and the research challenges and opportunities related to studying this growing population of breast cancer survivors.

The Nature of Metastatic Breast Cancer Today

Of the more than 232,000 cases of female breast cancer in 2014, only 5 % of white women and 8 % of African American women are expected to be diagnosed initially with stage IV breast cancer (Siegel et al. 2014). For many of these women metastatic disease at presentation is occult and is identified due to aggressive staging, although a substantial number have clinically apparent and symptomatic disease. Very little attention has been devoted to newly diagnosed stage IV patients in terms of their presentation characteristics and psychosocial needs. An interesting and provocative analysis by Johnson et al. (2013) suggested that while the incidence pattern of stage IV disease at diagnosis has been stable among women older than 40 years, it has steadily increased among younger women, with estrogen receptor positive disease accounting for much of the increase. Approximately 12,000 newly diagnosed women enter the ranks of those living with metastatic breast cancer each year.

In contrast, it is exceedingly difficult to find data on the number of women who are living with metastatic cancer as a result of recurrence—that is, how many are newly recurrent each year for the first time (incidence) and the prevalence of women living with recurrent metastatic disease. As one breast cancer advocate for patients with metastatic breast cancer commented to us, “If we are not counted, we do not exist.” The nature of metastatic disease varies substantially, with local recurrences on the chest wall or skin that may seem limited, but can be a potential harbinger of more distant disease. More often, recurrences are in regional or distant sites, and are usually identified due to symptoms. Patterns of recurrence vary depending on the initial tumor characteristics. Hormone receptor positive tumors can have very late recurrences, often decades later. Thus the period of risk for recurrence can be lengthy, especially in younger women for whom competing causes of death are less frequent; for younger women, breast cancer is most often the cause of death, in contrast to older women (Early Breast Cancer Trialists' Collaborative Group 2005). Thus, women living with metastatic breast cancer for long periods of time may have a higher representation of younger women than for incident breast cancer. With these two sources of women living with metastatic cancer (incident stage IV and recurrent breast cancer), some have estimated that there may be as many as 160,000 women and men living with metastatic disease (http://mbcn.org/education/category/most-commonly-used-statistics-for-mbc), but this estimate is uncertain.

Just as we now recognize multiple genomic subtypes of breast cancer at diagnosis, these subtypes can play out in different patterns of metastatic disease (e.g., early vs. late recurrence; soft tissue vs. visceral disease; bone dominant). The options for therapy will depend not only on the site and pattern of disease, but the disease-free interval, what prior therapy has been given, and whether or not endocrine or HER 2-directed therapies are appropriate and available. Unlike the situation several decades ago, we now have many additional endocrine therapies, and the ability to use several sequential HER2-directed therapies has completely transformed what was a rapidly fatal form of breast cancer. In addition, women with isolated ipsilateral local recurrence that is excised have a survival benefit from the reintroduction of chemotherapy, particularly in the setting of hormone receptor positive disease (Aebi et al. 2014). Thus, the treatments and outlook for women living with metastatic breast cancer today are varied, with some subsets of women living for extended periods of time with stable, well controlled disease, and others requiring continuous and serial therapies, with only modest responses. It is therefore difficult to generalize about the medical aspects of living with metastatic breast cancer.

While this chapter could focus on the important issues associated with end-of-life care for women with advanced metastatic breast cancer, we have chosen instead to address the complexities of survivorship for breast cancer patients who are living with disease over extended periods of time from years to decades. As recently recognized in the Institute of Medicine report on the Delivery of High-Quality Cancer Care (Institute of Medicine 2013), palliative and psychosocial care services should be delivered to all patients with advanced cancer, as part of cancer care. We will assume that we will strive toward this goal in all women who are living with metastatic breast cancer, and in the sections below, focus on the consequences of enduring ongoing disease-directed therapy in this setting.

The Metastatic Disease Experience and Consequences of Long-Term Therapy

Just as the medical presentation of metastatic breast cancer is heterogeneous, so too is the psychosocial experience for women living with the disease. Some women are confronting cancer for the first time, others with recurrent disease are able to live for many years on stable, well-tolerated medical regimens, and yet others live with a moving target of more aggressive disease with arduous treatments and variable response. The psychological common denominator is the experience of profound life threat and concomitant uncertainty, for both the affected woman and her loved ones. Maintaining a balance of attending to threatening and difficult thoughts, feelings, and requisite medical demands while pursuing a meaningful and rewarding life, is a major task of living with metastatic disease. Another common psychological experience includes the need to alter major life goals as the cancer and its treatment impinge on the ability to function in central roles or as one pursues specific cherished life priorities while at the same time contending with limited energy.

Interpersonal challenges include garnering effective support and dealing with concerns for the well-being of close family, children, and friends. In qualitative interviews of women with recurrent breast or gynecologic cancer, most women reported receiving emotional support from family and friends. Erosion of social support also was evident, however, in perceptions of intentional distancing by some close others, others' lack of understanding that recurrent cancer indicates a chronic illness, and women's curtailing their requests for support so as not to burden others (Thornton et al. 2014).

These and other challenges of living with metastatic disease are summarized in Table 16.1. Some of the tasks overlap with those encountered by women managing early-stage disease, but often are intensified in women with metastatic breast cancer (e.g., fatigue), and others are unique to the experience of metastasized disease, such as accepting stable disease as a desirable outcome of treatment. Particularly frequent or severe problems are addressed in this section.

Pain and fatigue are the two most common symptoms experienced by women living with metastatic breast cancer. Pain is often the first symptom of recurrent breast cancer; in women with stage IV disease at diagnosis, it may also be a presenting symptom. Pain can result from the after effects of initial breast cancer surgery and radiation, as well as in association with local recurrence and/or lymphedema. The latter may produce both psychological consequences and physical sequelae, such as arm heaviness and pain. Bone metastases and skeletal events (e.g., fractures) have become less frequent with bisphosphonate therapy; however, women still may suffer from severe pain and limitation of function as a result of bone metastases and nerve entrapment syndromes. Fortunately, skeletal metastases are often very responsive to radiation as well as analgesics, but the chronic and ongoing nature of pain when metastatic disease is in the bones can be burdensome. Similarly, visceral disease (e.g., liver, intra-abdominal or thoracic) can be responsible for substantial pain that is often more challenging to control. Cumulative toxicities from chemotherapy and radiation therapy can also contribute to pain syndromes, such as post-taxane neuropathy and radiation fibrosis and nerve entrapment. Scar tissue can lead to functional limitations and associated pain.

Among the challenges of pain management in women living with metastatic disease is their desire to be alert and functional, and not be dragged down by the sedation of narcotics. Many women continue to work and actively manage their households, and their reluctance to take analgesics on a regular basis may reduce the quality of their pain control. Complementary and alternative medicine (CAM)

Table 16.1 Adaptive tasks faced by women with metastatic breast cancer[a]

Physical and medical challenges
Managing physical symptoms and side effects (e.g., pain, fatigue)
Dealing with constant or changing treatment schedules
Accepting stable disease as a desirable outcome of treatment
Maintaining adequate communication with the medical treatment team
Fearing abandonment by the medical team
Deciding to end curative treatment and accepting palliative care
Psychological challenges
Coping with uncertainty and unpredictability
Perceiving a lack of control
Fearing dependency on others
Progressively losing functional ability
Maintaining valued life goals
Fearing death and suffering
Balancing hope with realistic preparations for the future
Managing complex emotions
Having unmet informational needs
Interpersonal challenges
Communicating with friends and family about illness and death
Feeling socially isolation and lacking emotional or instrumental support
Having concerns for loved ones
Spiritual and existential challenges
Making sense of and accepting the cancer diagnosis in the context of spiritual beliefs
Finding meaning in one's life and death
Practical concerns
Knowing when and how to seek home help, transportation assistance, or other services
Managing financial and legal affairs

[a] Adapted from Low et al. (2007) with permission

approaches are used by many women, although systematic and evidence-based data are lacking. Cancer-directed therapies will often relieve pain, e.g., radiation, chemotherapy. CAM therapies may help with management of treatment side effects as well. Because women living with metastatic breast cancer are hopeful for treatment responses, they are highly motivated to find a therapy that will relieve pain as well as prolong life. Some women move through serial treatments and look for experimental opportunities.

Fatigue, which is another serious problem for women living with metastatic breast cancer, is multi-factorial; contributors include the disease itself, treatments, and probably deconditioning from the physical symptoms associated with the disease. Proinflammatory cytokines, frequently elevated in advanced cancer (de Raaf et al. 2012), may be responsible for cancer-related fatigue that can seem out of proportion to the tumor burden. In addition, chemotherapy, radiation, and many of the newer targeted therapies (e.g., everolimus) can contribute to ongoing fatigue (Baselga et al. 2012). Although physical activity may be effective in relieving cancer-related fatigue in patients with less tumor burden, in patients with metastatic disease, some balance of energy conservation and physical activity may be the most appropriate strategy (Howell et al. 2013). CAM therapies such as yoga and Tai chi may be effective, but may have to be done cautiously in the setting of bone metastases.

Table 16.2 Factors associated with poor psychological adjustment in the context of metastatic breast cancer[a]

Severe physical symptoms (especially pain) and poor functional status
Younger age
Low dispositional optimism
Low perceived social support
Suppression of emotional experience or expression
High coping through avoidance and low coping through approach-oriented strategies

[a] Adapted from Low et al. (2007) with permission

Clinically significant depression, anxiety, and adjustment disorders are prevalent in adults with advanced cancer (Miovic and Block 2007) and in women with recurrent or metastatic breast cancer specifically (Burgess et al. 2005; Okamura et al. 2000). For example, in a 5-year study of women diagnosed with early-stage breast cancer within 5 months of study entry (Burgess et al. 2005), depression and anxiety diagnosed via interview using standard diagnostic criteria were more prevalent (45 %) in the 3 months following diagnosis of recurrent cancer than after initial breast cancer diagnosis (36 %). Cancer-related distress, in the form of intrusive thoughts and feelings about the disease, also is elevated after diagnosis of recurrent breast cancer (Andersen et al. 2005; Oh et al. 2004). Whereas cancer-specific distress and general quality of life improve over the year after diagnosis, problems with physical symptoms and functioning persist (Yang et al. 2008b). Although very few longitudinal studies are available, attributes associated with poorer psychological adjustment in women with recurrent and metastatic disease (see Table 16.2) include such factors as younger adult age, more severe physical symptoms (e.g., pain, fatigue), low social support, and more coping with the cancer experience through avoidance and less approach-oriented coping (e.g., planning, positive reappraisal; Yang et al. 2008a).

Certainly, a diagnosis of metastatic breast cancer generates psychological, interpersonal, and physical demands. It appears, however, that most women maintain or recover generally positive psychological health. In addition, adults with advanced cancer report that benefits such as enhanced relationships, deepened spirituality, and strengthened life appreciation and priorities can accompany the experience (Moreno and Stanton 2013).

Care of Women with Metastatic Disease

Women living with metastatic breast cancer have frequent and ongoing contact with the oncology care system. Initial treatment planning should be multidisciplinary, as is recommended for initial diagnosis and treatment (Cardoso et al. 2012). Even when disease is controlled and stable, as with responsive endocrine sensitive cancer, regular visits to the oncologist will occur at least every 2–3 months. Monitoring of disease status will often focus on tumor markers and specific scans, and patients may have need for symptomatic management of disease-related or treatment-related symptoms. Often, women will be able to continue working and do other meaningful activities, but some may have serious fatigue, cognitive difficulties or pain that may make activities difficult.

Living with the uncertainty of how long a specific treatment regimen will provide benefit is one of the critical challenges that the patient and her physician must face. The tempo of the disease recurrence as well as the burden of metastatic disease sites (a few or many; soft tissue vs. visceral) will provide some indication of whether or not complex multi-agent therapy is recommended or single agent serial treatments are appropriate. Increasingly, the approach to metastatic disease (Cardoso et al. 2012) reflects the consensus that palliative and supportive care are essential, and that the patient's preferences need to be taken into consideration (Table 16.3 from Cardoso). In addition, a recent consensus panel outlined specific strategies for addressing the supportive and palliative care needs of women living with metastatic disease, from a global perspective, with organ-specific approaches (Cleary et al. 2013). However, most of these recommendations are consensus based, with few randomized studies available.

Table 16.3 Guideline statement for management of advanced breast cancer (ABC)[a]

(1) The management of ABC is complex and, therefore, involvement of all appropriate specialties in a multidisciplinary team (including but not restricted to medical, radiation, surgical oncologists, imaging experts, pathologists, gynecologists, psycho-oncologists, social workers, nurses, and palliative care specialists), is crucial

(2) From the time of diagnosis of ABC, patients should be offered appropriate psychosocial care, supportive care, and symptom-related interventions as a routine part of their care. The approach must be personalized to meet the needs of the individual patient

(3) Following a thorough assessment and confirmation of MBC, the potential treatment goals of care should be discussed. Patients should be told that MBC is incurable but treatable, and women can live with MBC for extended periods of time (many years in some circumstances). This conversation should be conducted in accessible language, respecting patient privacy and cultural differences, and whenever possible, written information should be provided

(4) Patients (and their families, caregivers or support network, if the patient agrees) should be invited to participate in the decision-making process at all times. When possible, patients should be encouraged to be accompanied by persons who can support them and share treatment decisions (e.g. family members, caregivers, support network)

(5) There are few proven standards of care in ABC management. After appropriate informed consent, inclusion of patients in well-designed, prospective, randomized trials must be a priority whenever such trials are available and the patient is willing to participate

(6) The medical community is aware of the problems raised by the cost of ABC treatment. Balanced decisions should be made in all instances; patients' well being, length of life and patient's preference should always guide decisions

(7) Validated patient reported outcome measures provide useful information about symptom severity and the burden and the impact of these symptoms on overall quality of life. Systematic collection of such data should be integrated with other clinical assessments and form part of the decision-making about treatment and care

[a] Adapted from Cardoso et al. (2012) with permission. MBC is metastatic breast cancer

Compared with efficacious psychosocial interventions tested in randomized controlled trials (RCTs) for adults with early-stage cancer (e.g., Faller et al. 2013), the number of trials for women with metastatic disease is small. Women with metastatic breast cancer often are not included or included in such small numbers in those trials that reliable subgroup analyses are not possible. A recent review and meta-analysis of ten psychological RCTs with 1,378 women diagnosed with metastatic breast cancer included three trials of distinct individual approaches and seven group psychotherapy trials (four supportive-expressive therapy trials and three cognitive-behavioral trials) (Mustafa et al. 2013). Although some trials produced psychological benefit, the meta-analysis did not yield a clear pattern of psychological effects, given that a wide variety of outcome measures and follow-up durations were used. Across three trials, however, supportive-expressive group therapy produced a significant reduction in pain compared to usual care. In addition, there was some evidence of a survival benefit associated with intervention participation at 1 year (six trials) but not at 5 years (four trials) after the interventions.

Research Challenges and Opportunities

The most pressing challenge today is the lack of systematic research on women living with metastatic breast cancer for lengthy periods of time. Although many women have a relatively rapid progressive course from inception of metastatic recurrence to end-of-life care, there are both intermediate and long-term survivors for whom we have little information about their disease trajectory and experience of living with ongoing therapy that includes disease-related symptoms and treatment toxicity. For example, at one extreme, women who experience an ipsilateral breast cancer recurrence may have a variable course, with a continuous risk of recurrence after tumor excision that can be improved with the addition of adjuvant chemotherapy, especially in patients with estrogen receptor negative tumors in the CALOR trial (Aebi et al. 2014). Five year disease-free survival in those treated with chemotherapy was 69 vs. 57 % in those who did not receive chemotherapy. When multiple site metastatic recurrence occurs, the outcomes are less favorable, although durable periods of remission may occur for those with limited soft-tissue and bone-dominant disease that is hormone sensitive, as well as with patients for whom both endocrine and HER 2 targeted therapies are available. The major challenge for researchers is to be able to identify these patients and engage them in trials. The CALOR trial took many years to accrue and closed without meeting its initial accrual goal. In our own experience in a major metropolitan area, it also is difficult to recruit women living with metastatic disease for studies of psychosocial outcomes. Why do we have such a limited database? What are the issues we should study?

Adequate assessment of quality of life, cancer- and treatment-related symptoms and side effects, health behaviors, and psychosocial status is essential in women with metastatic disease. Patient-reported outcomes, such as quality of life and symptoms (e.g., fatigue, pain), are important targets of intervention as well as indicators of prognosis in metastatic disease (Gotay et al. 2008; Quinten et al. 2011). Especially in the context of metastatic disease, in which energy to complete assessments might be limited, development of measures that are brief, reliable, and valid is vital. For example, the Patient-Reported Outcomes Measurement Information System (PROMIS) contains a number of pertinent measures (e.g., fatigue, pain, depressive symptoms, anxiety; Alonso et al. 2013) for use in research and clinical practice. Psychometrically sound and valid assessments of experiences specific to women with metastatic disease also are needed.

One of the most important opportunities and challenges we face in management of metastatic breast cancer is the integration of palliative care into standard disease management. Because treatment for metastatic breast cancer often involves both medical and radiation oncologists, those specialists are looked to as the managers of care. Many women resist consideration of pain and symptom management while they are undergoing active treatment, such that referral to palliative care specialists does not occur until late in the treatment of metastatic disease. Breast cancer patients living with metastatic cancer are often interested in exploring experimental therapies and may perceive referral to palliative care as an indication of the oncology care team giving up on their cancer-directed care. To the extent that palliative care is integrated into cancer-directed treatment from the time of metastatic recurrence, symptom management and psychological concerns can be effectively co-managed without a sense of abandonment or change in course (Smith et al. 2012; Von Roenn 2013) (see Fig. 16.1).

Other major concerns for patients living with metastatic disease involve how best to live with the disease. Should they continue working? Can they afford their medical care? On whom do they rely for social support, especially as their health declines? Do they have an aging spouse or young children who require care?

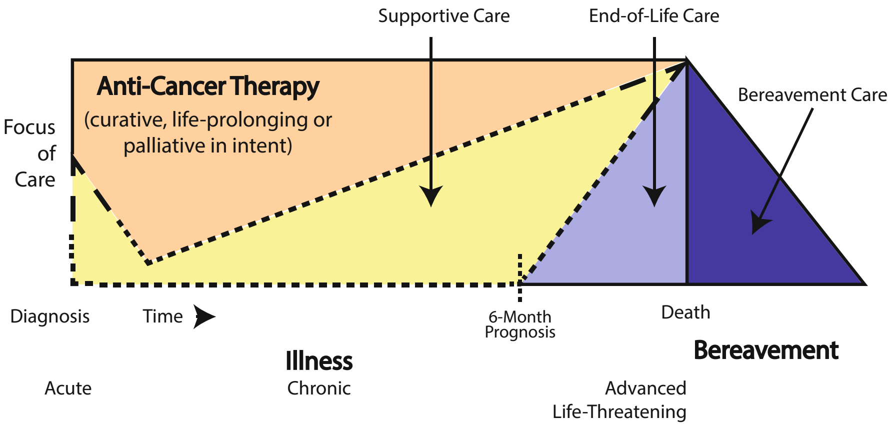

Fig. 16.1 Comprehensive cancer care [Adapted from National Cancer Institute. EPEC™-O. Education in palliative and end-of-life care for oncology. Available at : http://www.cancer.gov/cancertopics/cancerlibrary/epeco. Accessed 20 Sept 2014]

Table 16.4 Key elements of individualized care for patients with advanced cancer[a]

1. Patients should be well informed about their prognosis and treatment options, ensuring that they have opportunities to make their preferences and concerns regarding treatment and supportive care known
2. Anticancer therapy should be discussed and offered when evidence supports a reasonable chance of providing meaningful clinical benefit
3. Options to prioritize and enhance patients' quality of life, should be discussed at the time advanced cancer is diagnosed and throughout the course of illness along with development of a treatment plan that includes goals of therapy
4. Conversations about anticancer interventions should include information on likelihood of response, the nature of response, and the adverse effects and risks of any therapy. Direct costs to the patient in terms of time, toxicity, loss of alternatives, or financial impacts that can be anticipated should also be discussed to allow patients to make informed choices
5. Whenever possible, patients with advanced cancer should be given the opportunity to participate in clinical trials or other forms of research that may improve their outcomes or improve the care of future patients
6. When disease-directed options are exhausted, patients should be encouraged to transition to symptom-directed palliative care alone with the goal of minimizing physical and emotional suffering and ensuring that patients with advanced cancer are given the opportunity to die with dignity and peace of mind

[a] Adapted from Peppercorn (2011)

Unfortunately, all the resources that have been brought to bear for breast cancer survivors, that is, patients diagnosed with early stage disease and treated with curative intent who are living disease-free, do not seem to be suitable for women who are living with chronic and active cancer. Advance care planning is especially important for women living with metastatic breast cancer, yet it can remain unaddressed, primarily because of the slower trajectory of advancing disease, and the serial effective therapies that are available and offered to these patients (Peppercorn et al. 2011). Essential elements of that care are described in Table 16.4. Much more research is needed in women living with advanced breast cancer to determine how best they can maximize physical, emotional and spiritual well-being, while addressing their advance care planning needs.

Effective approaches to prevent and address cancer-related symptoms and side effects, as well as to promote positive psychosocial adjustment, are crucial for women living with metastatic breast cancer. Current evidence suggests that supportive expressive group therapy is effective for easing pain in this group (Mustafa et al. 2013), but strong evidence is lacking for the effects of interventions on other symptoms and psychosocial outcomes. To the extent that they address problems experienced across the cancer trajectory, efficacious psychosocial interventions (Faller et al. 2013) might generalize to women with advanced disease. Women with metastatic breast cancer can face distinct or more severe problems (e.g., life goal adjustment, progressive loss of function), however. Therefore, unique intervention approaches for women with metastatic cancer require development. In addition, disseminable approaches are needed which are readily accessible for women who might be experiencing physical compromise as a result of metastasized cancer and its treatment and therefore cannot attend in-person treatment regularly. For example, we recently found that, compared to standard care, an intervention (Project Connect Online) designed to facilitate personal website development and use to communicate with friends and family about the breast cancer experience produced improvements in depressive symptoms, positive mood, and life appreciation. Effects of this online intervention were particularly evident for breast cancer patients in active medical treatment, most of whom had metastatic disease (Stanton et al. 2013). Clearly, much work remains to promote quantity and quality of life and health for women who live with metastatic breast cancer.

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