Evidence Report

Chapter 1. Introduction

This evidence report by the University of Ottawa's Evidence-Based Practice Center (UO-EPC) describes the results of a systematic review of the scientific-medical literature designed to survey the range of quality measures assessing the quality of breast cancer care in women, and to characterize specific parameters potentially affecting their suitability for wider use. Specific emphasis was placed on diagnosis, treatment (including supportive care), followup, and the reporting/documentation of this care. The population of interest was female adults diagnosed with, or in treatment for, any histological type of adenocarcinoma of the breast, including both in situ and invasive cancer. This report was requested by a Federal collaboration comprising the Agency for Healthcare Research and Quality's (AHRQ) Center for Quality Improvement and Patient Safety (CQuIPS), the National Cancer Institute (NCI), the Centers for Disease Control and Prevention (CDC), and the Centers for Medicare and Medicaid Services (CMS). The National Quality Forum (NQF) is joined with these Federal agencies in a public-private initiative to identify and promote the use of evidence-based quality measures of cancer care. In addition to informing the research community and the public on the availability and utility of quality measures of breast cancer care, it is anticipated that the findings of this report will be used to help define an agenda for future research.

In this chapter, terms central to the present project are defined, followed by a brief overview of the burden of breast cancer, its range of care, and issues concerning the latter's documentation. The topics of breast cancer screening and prevention will be addressed in a separate task order. Subsequent chapters describe the methods used to identify and review studies, the cataloguing and appraisal of attempts to measure the quality of breast cancer care, and recommendations for future research in this area.

Overview of the Healthcare Quality Received by Americans

The quality of healthcare refers to "the degree to which healthcare services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[1] It is estimated that more than one trillion dollars is spent annually on healthcare in the United States, yet there are few systematic and comprehensive data on how well this care is provided by practitioners, organizations, and systems.[2] Various sources (e.g., healthcare professionals, hospitals, health plans) have provided some data on healthcare, including its quality. However, the absence of a coordinated national quality measurement and reporting system has meant that these data are likely too inconsistent and incomplete to permit derivation of a national overview of problems in healthcare quality that could potentially serve to inform the public about the quality of its healthcare choices.[3]

Nevertheless, two recent publications have suggested that the quality of healthcare received by Americans is less than ideal.[4,5] For example, in a survey of 30 health conditions ranging from osteoarthritis to prenatal care, McGlynn et al. observed that, on average, Americans have received about half (54.9%) of the recommended medical care processes.[5] They also noted greater problems with underuse (46.3% of participants failed to receive recommended care) than

Note: Appendixes and Evidence Tables cited in this report are provided electronically at http://www.ahrq.goc/clinic/epcindex.htm

with overuse (11.3% received care that was not recommended, some of which was potentially harmful). These are important findings given that they are based on a comprehensive view of the healthcare quality received by a representative sample of the American population across a broad spectrum of conditions, rather than on some narrowly defined healthcare condition, care, or population.

In the study by McGlynn and colleagues, a total of 439 standards of care, or quality indicators, represented 30 acute and chronic conditions, in addition to preventive care.[5] For each of the health conditions, data were presented as aggregates, including as few as three (i.e., osteoarthritis) and as many as 39 indicators of quality care (i.e., prenatal care). Adherence to the aggregate indicators ranged from 10.5% for alcohol dependence, to 78.7% for senile cataracts. The breast cancer care data are systematically reviewed in this report.

Although the reported adherence rates may have been somewhat higher had McGlynn et al. used data sources other than medical records supplemented with interviews regarding participants' health history (e.g., audiotapes of encounters), their overarching observation highlights a gap between ideal and actual care—that is, between what evidence has identified as recommended care and what Americans actually receive.[5] McGlynn et al. point out that such a deficit endangers the health and well-being of the American public. However, they also acknowledge that there are ways to begin to change this state of affairs.

An important first step would be to collect, synthesize, and make available data regarding the performance of healthcare professionals and healthcare systems.[5] This information would help to identify specific problems with healthcare quality, to establish bases upon which to determine accountability, and to serve as the focus of research to develop new knowledge about healthcare systems. In addition, these data could serve as a national baseline against which results of attempts to improve the quality of care could be compared.[6,7] Accountability, improvement, and research constitute the three broadly stated purposes of quality measurement.[8] Attempts to collect performance data could shed light on the overuse, underuse, misuse, or wide variability in use of care,[6,9] ultimately contributing to correcting disparities in the quality of care received by different populations or subpopulations.[10]

The Measurement of Healthcare Quality

The measurement of healthcare quality begins ideally with the establishment of an evidence-based performance standard, or criterion, relative to which adherence data can be ascertained.[11] Such a standard is an indicator of quality care, or a "quality indicator" (e.g., radiotherapy after breast-conserving surgery). An evidence-based standard is one supported by study evidence, not mere opinion or conjecture, demonstrating that this care is linked to improved patient outcomes.[12]

Identifying a quality indicator ideally requires a systematic review of the pertinent scientific-medical evidence, followed by an expert panel consensus process to ensure that the recommended care highlighted by the synthesis of findings is clinically relevant, up-to-date, and practical to deliver. Without a systematic review process to minimize or correct for possible bias, both in the way in which relevant evidence is captured and appraised (e.g., multiple appraisers of data) and in the evidence base itself (e.g., reviewing unpublished material with the potential to influence a synthesized result), a peer consensus process can draw a skewed conclusion based on idiosyncratic interpretations of the evidence base, including appraisals of

subsets of data. A recent study found that, without the findings of a systematic review process to guide it, participants in a consensus conference process merely relied on their favourite articles to substantiate their views.[13]

The quality indicators employed by McGlynn et al. in their recent comprehensive study[5] were derived systematically and rigorously using RAND's Quality Assessment Tools system.[14] After RAND staff identified conditions representing the leading causes of illness, death, and utilization of healthcare, RAND staff physicians systematically searched the medical literature (via Medline) and reviewed related established national guidelines. Following this, quality indicators were proposed.[15] Nine-member, multispecialty expert panels then assessed the clinical appropriateness of the quality indicators using the RAND-UCLA modified Delphi method.[16] Ten evidence-based quality indicators pertaining to breast cancer care were derived, with one evaluating breast cancer screening.[17]

This rigorous, evidence-based process accurately illustrates what is required to systematically develop quality indicators for use in quality measurement.[17] Questions concerning the quality of healthcare can then be evaluated by measuring the adherence to these standards of care. An example of such a question is: "how many women qualifying to receive a standard of breast cancer care (i.e., by virtue of their clinical situation) actually receive it (in timely fashion)?" Or, from the healthcare provider perspective, "how many healthcare professionals, when attending to women qualifying to receive a standard of breast cancer care (i.e., by virtue of their clinical situation), actually deliver it (in timely fashion)?"

Yet, an additional step determines whether or not the quality indicator used as the performance standard to assess adherence can be considered a formally-, or fully-developed quality measure, that is, one which exhibits the scientific properties required to instil confidence in the observations it generates.[18] Two key properties of a quality measure are "reliability" and "validity." Data referring to other properties, such as sensitivity (i.e., how sensitive a diagnostic test is at detecting disease) or specificity (i.e., how good a test is at rejecting samples that are not diseased), were not identified by the present review.[18]

When a measure is said to be reliable, it means that if multiple observers, or the same observer (at different points in time), implement this measure, the observations it yields should be highly consistent, if not identical. "Reliability" asks whether the observations produced by the measure are repeatable, or reproducible, across different situations.[18] For example, would a diagnostic test of cancer yield the same observation when administered two times, 6 hours apart? Reliability is thus a key characteristic of a measure.

The validity of a measure, and hence its measurements, is closely related to its reliability. "Validity" asks whether the measure is assessing what it was intended to measure.[18] For example, does a diagnostic test accurately, and only, measure the characteristic known to indicate the presence of cancer? Or, does the depression scale accurately and exclusively measure the signs and symptoms of depression? If the measure has a history of exclusively generating empirical evidence regarding the target characteristic, then it is considered valid. Without evidence to support its validity, it does not matter how perfectly or how often independent observations afforded by this measure actually agree, because what it quantifies may not be what the user intends it to measure. For example, a purported measure of depression may actually identify reliably the signs and symptoms of anxiety.

Prior to the dissemination and wider use of quality indicators as standards against which to measure adherence to recommended health care, a formal scientific process to establish the requisite properties is thus recommended. With respect to breast cancer, for example, this means

defining a quality indicator, or standard, using appropriate evidence, followed by establishing its reliable and valid use through pilot-testing with data sources containing breast cancer care data (e.g., medical records, cancer registries).[18]

In the absence of consistent and strong data concerning each of these two "psychometric" properties, it is difficult to interpret the meaning of quality measurements with any confidence. Thus, while it can be argued that any attempt to measure adherence to a quality indicator amounts to quality measurement, unless the indicator is subjected to a scientific-validational process by which any measure should be developed, and where evidence for each property is shown to be strong and consistent, the measure cannot be considered to be a sound (i.e., reliable and valid) one. A quality measure's scientific soundness, and thus its advantage over an unvalidated one, is conferred by these properties.[9] Three other criteria with which quality measures can be evaluated are described in The Ideal Quality Measure section in this chapter. More is said about the validational process in the Discussion.

The following example is taken from AHRQ's National Quality Measures Clearinghouse (NQMC) web site.[8] Since it focused on breast cancer screening, it was not eligible for inclusion in the present review. The quality indicator is expressed as "women 50-69 years of age having one or more mammograms during the measurement year or the year prior to the measurement year." The quality indicator asserts the standard, or recommended, care. From this, the quality measure is defined as: "the percentage of women 50-69 years of age who had one or more mammograms during the measurement year or the year prior to the measurement year." It quantifies adherence to the standard.

Each element of the definition is clearly and specifically described. These include the population to which the indicator applies, and the time frame. But, on the NQMC web site there is also a clear indication of those women for whom this standard should not be applied (e.g., women who had a bilateral mastectomy and for whom administrative data do not indicate that a mammogram was performed). The specificity, completeness and clarity of the wording of a quality indicator are necessary to assure that different users share the same meaning, and thereby yield the same or consistent observations (i.e., its "reliability" as a measure) when, on different occasions, they consult specific data sources (e.g., medical records) to obtain adherence data; and, that these observations unambiguously reflect what the quality indicator was intended to identify (i.e., its "validity" as a measure).

The NQMC web site also provides information on the relevant data sources (i.e., administrative data, and medical records), as well as a description of any allowances for patient factors (i.e., this quality measure requires that separate rates be reported for commercial, Medicare, and Medicaid plans). While having all these details made explicit may contribute to consistent observations, the extent of the testing of the quality measures was described as "unspecified," raising doubts that reliability and validity data had ever been obtained for this quality measure via a formal validational process.

Thus, in light of this example, a formal definition of a quality measure, and how it differs from a quality indicator, can be stated. A quality measure may be defined formally as a mechanism to quantify the quality of a selected aspect of care by comparing it to a criterion (e.g., "percentage of women 50-69 years of age who had one or more mammograms during the measurement year or the year prior to the measurement year").[8] One practical understanding is that it is a mechanism to quantify the degree of adherence to a standard of care, or quality indicator (i.e., "women 50-69 years of age having one or more mammograms during the measurement year or the year prior to the measurement year"). A quality indicator essentially

becomes a quality measure in the act of measuring adherence to this standard. According to McGlynn:

> Quality measures generally consist of a descriptive statement or indicator…, a list of data elements that are necessary to construct and/or report the measure, detailed specifications that direct how the data elements are to be collected (including the source of data), the population on whom the measure is constructed, the timing of data collection and reporting, the analytic models used to construct the measure, and the format in which the results will be presented. Measures may also include thresholds [minimal], standards, or other benchmarks of performance.[12]

Yet, what happens after a quality measure has been developed formally is also important. Studies should test the stability of the recommended care's links to improved clinical or patient-reported outcomes (e.g., survival, quality of life [QOL], satisfaction with care). Although improved outcomes initially helped support it, additional evidence for links to improved outcomes can reinforce the quality measure's clinical appropriateness and thereby justify its continued use. Subsequent applications to data sources could also reveal that its appropriateness is actually restricted to certain subpopulations (e.g., minority groups).

There are thus two meanings of the term "links to outcomes." First, a quality indicator needs to be supported by an optimal strength of evidence (i.e., the design types, power, quality/validity, effect sizes, and number of research studies) indicating that improved outcomes are associated with receipt of the type of care to which the quality indicator refers. Its links to improved outcomes essentially define the clinical "appropriateness" of this care. An abandoned attempt to investigate this definition of "links to outcomes" is described in Chapter 2.

Second, in studies quantifying the adherence to a standard, it may also be possible to prospectively or retrospectively obtain data regarding this care's links to patient outcomes. This would elucidate whether *study* patients receiving the standard of care experience improved outcomes when compared with those failing to receive it. This second definition of "links to outcomes" reflects one key aspect of the present project's scope.

Types of Quality Measure

There are various types of quality measure. Structural measures include characteristics of clinicians (e.g., years of experience, board certification), organizations or systems (e.g., type of available equipment, staffing patterns), and patients (e.g., type of insurance, severity of illness).[17] These measures reflect the elements of a healthcare delivery system, which precede the interaction of a clinician and a patient, and are implied by questions pertaining to the "availability" of a certain healthcare "capacity." Outcome measures of quality index changes in a patient's current and future health status, including functional status, QOL, and satisfaction with care.[17] In providing the patient perspective on quality of care, such measures can reflect the impact of a single intervention (e.g., a diagnostic procedure) or the cumulative effect of various types or processes of care.[8]

Process measures assess the degree to which a healthcare provider competently and safely delivers appropriate and timely care.[19,20] This includes the ways in which clinicians and patients interact (e.g., providing information, answering questions), as well as the appropriateness,

timeliness, and convenience of a medical intervention for a specific patient.[17] "Appropriate use" denotes receipt/delivery of care that is indicated (i.e., given specific, observed conditions or circumstances), and often within an optimal time period. "Quality" of use refers to how well the care is delivered. Ways of indexing a patient's attainment of timely and appropriate healthcare have also been called access measures.[8] Process measures are often used to evaluate adherence to recommendations from clinical practice guidelines,[8] a view consistent with the Institute of Medicine's definition of performance measures as methods or instruments to estimate or monitor the extent to which the actions of a healthcare practitioner or provider conform to practice guidelines, medical review criteria, or standards of quality.[21]

McGlynn et al.'s above-noted quality indicators were primarily of the process variety.[5] These types of measure more readily identify specific areas of care requiring quality improvement than do, for example, outcome measures.[22] The latter typically necessitate additional investigation to discover the structures or processes requiring quality modification. Nevertheless, to derive a comprehensive understanding of the quality of the delivery of healthcare, it is likely important to link, whenever possible, data obtained from measures of structure, process, and outcome, in addition to data relating to cost, or burden.[9]

The Ideal Quality Measure

Four sets of criteria can be used to evaluate quality measures,[6,8,12] and these are attributes of the ideal quality measure. Each one should be scientifically sound, important, usable, and feasible.

As introduced above, scientific soundness refers to the specific properties of a measure that allow for its consistent use, across various situations, to observe what is intended (i.e., reliability and validity). This requires that the measure's description be precise and detailed. However, seen in light of the example from AHRQ's NQMC web site, quality measurement can merely entail the definition of a quality indicator as a standard against which performance is measured—that is, without the implementation of a formally developed quality measure with strong and consistent evidence for its reliability and validity. Thus, although any synthesis of the quality measurement literature will likely identify evidence derived from the two basic approaches to measuring the quality of health care, that is, with and without the use of validated quality measures, this is, in all likelihood, an artificial dichotomy. In spite of our illustration of two basic paths to achieve quality measurement (see Analytic Framework: Chapter 2), quality measures may be more realistically understood as being situated at various points along a trajectory of scientific development: from measures having received no formal development of their psychometric properties (e.g., reliability and validity), to those exhibiting weak or inconsistent evidence for these properties, and culminating ideally in reliable and valid quality measures. A scheme to evaluate the scientific soundness of each quality measure was derived for use in this review (see Trajectory of Scientific Development of Quality Measures: Chapter 2).

Following the definitions used in the domain of inquiry relating to the measurement of healthcare quality, for a quality measure to be "important" it must relate to an established national goal for quality care, represent a significant leverage point for achieving that goal, demonstrate that the quality of care is below standard or that there is considerable (e.g., demographic) variation in the quality of the provided care, or, show that the information produced by its application is useful for a stakeholder in the healthcare system.[12] The "usability"

of a quality measure denotes the meaningful interpretability of the observations yielded by its application and, whether or not, and how, such interpretations afford decisions and actions regarding the delivery of healthcare. Finally, a quality measure must be "feasible" to implement, that is, the data the measure yields should be readily available for collection within the normal flow of clinical care. A measure's feasibility is related to its adaptability, that is, its potential for appropriate use across various contexts and settings.

These four sets of criteria likely comprise a hierarchy by which quality measures can be appreciated:

> If a measure is not important, its other characteristics are less meaningful. If a measure is not scientifically acceptable, its results may be at risk for improper interpretations. If a measure is not interpretable, we probably do not care if it is feasible. If a measure is not feasible, alternative approaches to acquiring important information should be considered.[12]

Reasons for not being able to evaluate criteria other than scientific soundness are described in the Trajectory of Scientific Development of Quality Measures section in Chapter 2.

The President's Advisory Commission on Consumer Protection and Quality in the healthcare industry recommended the identification, development, and promotion of a common, or national, set of quality measures to assure accountability and quality improvement.[23] Yet, while measurement may be necessary, it is not sufficient to guarantee achievement of these objectives.[24] Barriers to the translation of evidence into accountability for, and improvements in, the safety, effectiveness, patient-centeredness, timeliness, efficiency, and equitableness of healthcare[4] include a lack of knowledge, skill, motivation, and resources available to those individuals, organizations, and systems who could bring about this change.[24] Solutions likely require modification of the ways in which health information is collected and reported.[5] James has suggested automating both data entry and its retrieval.[25]

Burden of Breast Cancer in Women

Other than skin cancer, breast cancer remains the most common cancer in women and the second leading cause of cancer-related death.[26] In the United States, it is estimated that, in 2003, over 211,000 women will be diagnosed with breast cancer, and approximately 40,000 will die from the disease.[26] Although much less common, breast cancer also occurs in men, accounting for less than 1% of all breast cancers (approximately 1600 cases in 2003).[26] According to data compiled by the Surveillance, Epidemiology and End Results Program (SEER), 1 in 8 women will develop breast cancer during their lifetime, with the risk increasing with age.[27] Although breast cancer occurs more often in white women than in black or Asian women, cancer survival rates have been estimated to be 15% lower in black women compared with white women.[27] Recent statistics (1992 - 1996) indicate that breast cancer-related deaths are declining, with the largest decrease observed in younger women, both white and black. The decline in death rates is attributed to earlier detection and improved treatment. Currently, it is recommended that all women over the age of 40 receive regular mammograms (every 1 to 2 years).[26,27] What follows is a brief overview of the range of breast cancer care, including some reference to available evidence.

Diagnosis

Primary Diagnosis

Suspicious breast abnormalities are often detected by women themselves, either during self-screening or by accident, or by clinical examination or routine mammography screening. A physical examination cannot, however, distinguish between a benign change and malignant tumor.[28] Although additional characteristics such as indistinct borders, skin dimpling or nipple retraction may indicate a malignancy, additional diagnostic techniques must be performed to confirm a diagnosis.[29,30]

Mammography remains one of the primary tools used to evaluate a palpable breast mass or other signs of breast disease although, in itself, it is not enough to diagnose a malignancy. In addition, mammography is not particularly useful for women with dense breast tissue—this is particularly true for younger women (i.e., under the age of 30), who tend to have dense breast tissue.[31]

Ultrasound has emerged as an important tool to assess a palpable mass in women with dense breast tissue and/or to complement mammography.[32,33] Ultrasound relies on high-frequency sound waves to form images of the breast, regardless of breast density. It is particularly useful at differentiating between solid-mass tumors and fluid-filled cysts, and hence it is often used to further evaluate suspicious abnormalities seen by mammography.

A number of additional imaging techniques, particularly magnetic resonance imaging (MRI) and positron emission tomography (PET), are sometimes also used, usually to complement mammography. They are employed to get more information about the abnormality and, if it is cancer, to determine if it has metastasized. Their usefulness as an alternative to mammography remains unclear.[34,35]

Although imaging techniques, particularly mammography and ultrasound, are used to suggest an initial diagnosis of breast cancer, a biopsy is performed to confirm the presence of cancerous cells. A biopsy is a procedure in which a sample of breast tissue is removed for microscopic examination by a pathologist. Breast biopsies assist physicians in confirming the presence of cancer cells, and if cancerous, the type and extent of the cancer. Breast biopsies can be removed using a needle or by surgery. There are many types of breast biopsy including: fine needle aspiration, core needle biopsy (ultrasound-guided, and stereotactic or X-ray guided), or surgical biopsy. Fine needle aspiration biopsy involves removing cells using a very thin needle, which is inserted into the suspicious tissue. A core biopsy uses a larger needle so as to remove actual pieces (cores) of breast tissue for microscopic analysis. Ultrasound or X-ray (stereotactic) guidance is used to locate the suspicious area of breast tissue. Stereotactic biopsy is used to biopsy very small areas such as microcalcifications or other suspicious areas that cannot be visualized on ultrasound. A surgical biopsy can be conducted when core needle biopsy is not possible, is inconclusive, or is discordant with imaging or expert opinion. A portion of the suspicious area may be excised and is known as an incisional biopsy, or, an excisional biopsy may be completed where the entire area is removed.

Secondary Diagnosis

Once breast cancer has been diagnosed, a number of tests are available to assess if and/or to what extent the primary breast cancer has metastasized to other parts of the body. X-rays of the

chest may be performed to determine if the cancer has spread to the lungs. Bone scans are performed to detect the presence of bone metastases. CT scans, PET scans and MRI are also available to assist in the staging of the cancer and to best guide the physician in choosing the best treatment option. Blood tests are also performed to detect the presence or absence of tumor markers that may indicate cancer activity in other parts of the body.[36]

Risk Factors

Although the cause of breast cancer is unknown, a number of factors are emerging as actual or potential risk factors. Risk factors make some people more likely than others, to develop a particular disease. Risk factors for breast cancer may include:

- Being female
- Increasing age
- Race
- Socioeconomic status
- Proliferative breast disease (atypical ductal hyperplasia, lobular carcinoma in situ)
- Personal history of breast cancer
- Family history of breast cancer
- History of mantle radiation
- Reproductive history (nulliparity, age at first live birth), age at menarche and menopause, history of breast feeding)
- Lifestyle (i.e., diet, alcohol, inactivity)
- Obesity after menopause
- Use of hormone replacement therapy

Most recently, the role of genetic factors has been more closely examined given the discovery that inherited alterations in the genes, BCRA1 and BRCA2, are linked to a predisposition to breast and/or ovarian cancer.[37,38] It has been estimated that approximately 5% to 10% of women with breast cancer have a hereditary form of the disease.[39] Most of these women have a strong family history of breast cancer, that is, close family members who have had breast and/or ovarian cancer, with the breast cancer having developed before the age of 50. For those considered to be high-risk, genetic testing is available to determine whether the woman carries the altered BCRA1 and/or BCRA2 genes.

Breast cancer prevention is becoming an important area of clinical practice, education and research. Breast cancer chemoprevention is the use of drugs (e.g., anti-estrogens) to lower the risk of developing breast cancer. For example, tamoxifen has proven to lower the risk of developing breast cancer in women considered to be high-risk.[40] Other options for lowering breast cancer risk include oophrectomy and prophylactic mastectomy. Women and their healthcare providers must carefully assess the risks and benefits of primary and secondary breast cancer prevention strategies, including the lowering of risk, and, risk-appropriate surveillance.

Treatment

There are essentially two approaches to the treatment of early breast cancer: localized (regional) treatment and systemic treatment. Local treatment specifically targets the breast and the adjacent lymph nodes. Options include surgery to remove the entire breast (mastectomy) or only part of the breast tissue containing the tumor and some of the normal surrounding tissue (lumpectomy or breast-conserving surgery), as well as radiation therapy (radiotherapy). Radiation therapy is highly focused, relying on a radioactive beam or radioactive "seeds" to locally destroy cancerous cells. Since the radiation is highly focused, side effects are limited to the area being treated.

Systemic treatment is directed to the entire body and is used to destroy any malignant cells that may have spread to other parts of the body. There are currently three different classes of systemic therapy: chemotherapy, hormonal therapy, and immunotherapy. Systemic therapy can be administered following surgery (adjuvant therapy) or before surgery, to reduce the size of the cancer (neoadjuvant therapy).

The decision on which treatment approach will be used depends on a number of prognostic factors that include: (1) stage of the cancer (2) whether it is an invasive or non-invasive cancer, and (3) whether the lymph nodes have been affected. Clinical staging of breast cancer is based on the TMN (tumor, node, metastasis) system, which assesses the size of the tumor, level of lymph node involvement, and the presence or absence of metastases.[41] In addition, the tumor is assessed for the presence or absence of specific prognostic tumor markers that will further guide the treatment protocol. Currently, tumors are assessed for estrogen receptor (ER) expression, and overexpression of the human epidermal growth factor receptor 2 (HER2) protein.

Treatment of advanced metastatic breast cancer specifically targets the relief of symptoms and maintenance of function and QOL. A number of treatments are considered for advanced breast cancer, including hormonal therapy and chemotherapy.[42]

Local Therapy

Surgery remains the primary treatment of choice for women with early breast cancer. Results of a recent 20-year followup study indicate that the longterm survival rate was the same among women who underwent breast-conserving surgery as for those who underwent radical mastectomies, suggesting that breast-conserving surgery is the treatment of choice for women with relatively small breast cancers.[43] However, the decision on whether the patient should have breast-conserving surgery or a mastectomy is made based on the size and pathological characteristics of the tumor. Patient choice should be considered and respected, particularly when surgical options have equivalent longterm benefits. For both surgical approaches, the

lymph nodes in the axilla closest to the cancerous breast are also removed (axillary node dissection). Removal of the lymph nodes, however, causes side effects in some patients, such as swelling in the arm (lymphedema). The removed breast and lymph tissues are then examined by a pathologist to ensure that enough of the cancerous tissue has been removed, and that there are no cancerous cells at the margins or outer edges of the tissue (i.e., clear surgical margins).

A relatively new, less invasive technique called sentinel lymph node biopsy involves the removal and examination of the sentinel nodes—the first lymph node(s) to which cancer cells are likely to spread from the primary tumor. If sentinel nodes are found to be positive, then the rest of the lymph nodes are removed in a lymph node dissection. A recent study has demonstrated that this procedure is as effective as axillary node dissection at detecting whether early breast cancer has spread, although it is not yet clear if it increases survival.[44] If the sentinel nodes are found to be negative, no further lymph node surgery is undertaken.

To reduce the risk of local recurrence, breast-conserving surgery should be followed by radiotherapy in order to eliminate any cancerous cells that may still be present in the breast tissue.[45] The Early Breast Cancer Trialists' Collaborative Group has concluded that, in women with early breast cancer, radiotherapy reduced the risk of local recurrence by two-thirds and produced an absolute increase in 20-year survival of approximately 2% to 4%. However, they estimated that the hazard risk associated with the treatment could reduce this 20-year survival benefit in young women.[45,46] Partial breast irradiation using brachytherapy implants (i.e., radioactive seeds placed directly into the tumor bed) or local intraoperative radiation may also provide local control,[47,48] although these techniques have not been evaluated in randomized trials. In some circumstances, radiation therapy also benefits patients treated with mastectomy.

Systemic Therapy

Adjuvant chemotherapies have been demonstrated to reduce the risk of recurrence and mortality in patients with early-stage breast cancer.[49,50] In the US, anthracycline-based regimens (e.g., doxorubicin, epirubicin) are the most widely-used for the treatment of early breast cancer.[51] The addition of taxanes, including paclitaxel, to adjuvant chemotherapy programs appears to improve disease-free survival rates[52,53] and overall survival rates when compared with anthracycline-based regimens alone.[51,52,54]

Adjuvant hormonal therapy is used to inhibit the effects of hormones such as estrogen and progesterone, which promote the growth of breast cancer cells. The anti-estrogenic compound, tamoxifen, is currently the most commonly used anti-estrogenic therapy (with or without chemotherapy) to treat both pre- and postmenopausal women with ER-positive primary breast cancer.[55] Adjuvant tamoxifen therapy is generally administered for five years in patients with hormone-receptor positive breast cancer.[51] Longterm followup of randomized controlled trials has indicated that, beyond 5 years of treatment with tamoxifen, there is no added benefit,[56-58] pending results of ongoing trials in Europe (i.e., ATLAS and aTTom trials). The benefit of adjuvant tamoxifen in women with ER-negative tumors remains to be determined.[59] Hormone suppression by ovarian ablation may also be considered in premenopausal women. Recently, the Early Breast Cancer Trialists' Collaborative Group concluded that, for women under the age of 50, ovarian ablation significantly improves longterm survival, at least in the absence of chemotherapy.[60] Further analysis is required to assess the relevance of ovarian ablation and hormone-receptor status.

Aromatase inhibitors (e.g., anastrozole, letrozole) are also emerging as an effective treatment option for ER-positive breast cancers in postmenopausal women.[61,62] However, there are limited data available regarding longterm toxicity.[63] Aromatase inhibitors bind to the aromatase enzyme, inhibiting the conversion of androgen to estrogen. Recent results of the NCI-C MA17 trial have shown a benefit, in terms of disease-free survival, for continuation of endocrine therapy with letrozole in women who remained free of disease recurrence after 4.5 - 6 years of adjuvant tamoxifen.[64,65]

Immunotherapy involves a relatively new class of agents that target the body's immune system. Currently, trastuzumab is the only immune therapy approved for the treatment of breast cancer. The FDA has approved it for the treatment of women with metastatic HER2-positive breast cancer or, through clinical trials, for women with early-stage HER2-positive breast cancer involving the lymph nodes.[66,67] Overexpression of HER2 protein results in increased cell division and a higher rate of cell growth. Trastuzumab is a monoclonal antibody that specifically binds to the HER2 protein, slowing the growth of HER2-expressing cells. It is estimated that HER2 is overexpressed in 25% of breast cancers.[68]

For patients with metastatic breast cancer, hormonal therapy (i.e., tamoxifen and/or ovarian ablation)[69] is considered in premenopausal women who are ER-positive; aromatase inhibitors are used for postmenopausal women. Both anastrozole and letrozole have recently been approved as first-line agents for the treatment of women with metastatic breast cancer, and trials are currently underway to investigate their potential as treatment for early breast cancer, both in the adjuvant and neoadjuvant setting.[70] For women with metastatic disease who are ER-negative, or those with rapidly progressive, life-threatening disease, or with visceral involvement, chemotherapy is indicated.

Neoadjuvant treatment with chemotherapy or endocrine agents is being used increasingly to downstage locally advanced and large operable breast cancers.[71-73] Neoadjuvant treatment may allow for inoperable breast tumors to become resectable, and for operable tumors initially requiring mastectomy to be successfully removed by breast-conserving surgery.

Followup

The goal of patient followup is to detect new or recurrent disease, and to assess treatment outcome. What constitutes followup care following primary breast cancer treatment, however, varies from center to center. In general, routine patient followup procedures include regular physical examinations, annual mammograms and pelvic exams.[74,75] Historically, followup has also entailed a more intensive diagnostic evaluation, including chest X-rays, bone scans, liver ultrasound, CT scan, and complete blood work (including cancer tumor markers) to detect early signs of disease recurrence. However, in women who do not report any symptoms that may indicate disease recurrence, these tests are currently not considered appropriate and cost-effective since they have not been shown to affect survival.[74-77]

In addition to clinical followup procedures, QOL issues are becoming an increasingly important part of the post-breast cancer treatment followup process.[78] Following primary breast cancer treatment, many breast cancer survivors experience longterm therapy-related complications (e.g., lymphedema, early onset menopause) that can have a significant impact on their QOL. For women who underwent a mastectomy, having lost a breast may have a significant impact on their emotional well-being. Concern about the breast cancer risk of family members, such as children, is a common apprehension of these women.

Supportive Care

The diagnosis of breast cancer is often accompanied by supportive care interventions, such as physical, emotional, spiritual, psychosocial and practical care. These are required to support women and their significant others through this distressing time.[79,80] Supportive care needs vary from individual to individual, and may change over time. The disease and its treatment may result in ongoing sadness, fear, anxiety and anger, and supportive care interventions often make an important difference to how patients cope with their illness over time.

Effective supportive care can be a component integral to producing an optimal treatment outcome in a patient with breast cancer. For example, preventing or controlling treatment-limiting side effects, such as nausea and vomiting, improves patients' QOL and allows greater tolerance of chemotherapeutic regimens.[81] This, in turn, may improve outcomes by preventing premature withdrawal from potentially life-saving chemotherapy regimens. For women with end-stage breast cancer, palliative care will include management of chronic pain associated with advanced disease, as well as other supportive care interventions.[82]

Reporting

The optimal management of patients with breast cancer relies on an accurate pathology diagnosis as well as appropriate monitoring and evaluation of the treatment program. Hence, reporting prognostically-significant information is critical. Standardizing the reporting with a typical set of data obtained from each patient, using the same terminology and diagnostic criteria, would facilitate this process. The adequate and complete documentation of treatment helps clinicians (and researchers) observe important covariations among clearly defined types of care and outcomes.