
Leveraging Comparative Effectiveness Research to Improve the Quality of Multidisciplinary Care for Breast Cancer Patients

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| Abstract | |
| Breast cancer is the most commonly diagnosed cancer among women. To date, the use of efficacy randomized controlled trials (RCTs) in breast cancer have resulted in dramatic improvements in oncologic outcomes for this disease. However, not every question pertinent to breast cancer is amenable to such efficacy trials. This chapter will discuss some of the unique aspects of breast cancer that make efficacy RCTs challenging and/or impractical, how comparative effectiveness research can be used to address these issues, and identify several key questions which would benefit from ongoing comparative effectiveness research. | |
| Keywords | |
| Comparative effectiveness research • Breast cancer • Breast conserving therapy (BCT) • Mastectomy • Sentinel lymph node biopsy • Axillary lymph node dissection • Hormonal therapy • Hormone receptor status | |

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1 Introduction

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer death for women in the United States. As a result of numerous randomized controlled trials (RCTs) addressing key breast cancer questions, great strides have been made in the detection, treatment, survival, and quality of life outcomes for this disease. However, not every question pertinent to breast cancer is amenable to such efficacy trials. There is also significant uncertainty in how the data generated in the highly-controlled clinical trial setting translates into “real world” practice. Comparative effectiveness studies are the optimal means of addressing both of these issues, and can generate critical evidence which complements the data generated through efficacy trials, potentially improving the quality of care we provide breast cancer patients. This chapter will begin with a brief representation of the critical role efficacy RCTs have played in breast cancer management, followed by a discussion of the unique characteristics of breast cancer which make some aspects of care difficult to assess with a RCT. We will next identify several important issues amenable to investigation with comparative effectiveness research (CER), and finally, discuss potential approaches which might lead to high-quality evidence for these issues.

2 The Roles and Limitations of Randomized Controlled Trials in Breast Cancer Research

Efficacy RCTs have played a critical role in advancing breast cancer care. With the enrollment of thousands of women across several decades, RCTs have been the driving force behind current best-practice guidelines for the multidisciplinary management of breast cancer. These studies were most commonly designed to compare oncologic endpoints (survival, recurrence, treatment adverse events) in selected patient populations receiving different therapies. The role of RCTs in defining the surgical management of breast cancer is especially noteworthy, with the evolution from the Halstead radical mastectomy to the current option of breast conserving therapy (BCT) with sentinel lymph node (SLN) biopsy (Fig. 1). The majority of these surgical trials have focused on overall survival and local recurrence. However, many surgical breast RCTs have increasingly incorporated alternative patient-centered outcomes, such as quality of life, [1] physical function, [2] and arm range of motion. [3].

However, even as we acknowledge the important role of RCTs in defining the management of modern breast cancer, it is important to recognize their limitations. RCTs are conducted within a tightly controlled environment with strict inclusion and exclusion criteria. Practically speaking, this may result in the exclusion of patients with unfavorable baseline characteristics, such as significant comorbidities or advanced age. As an example, in National Surgical Adjuvant Breast and Bowel

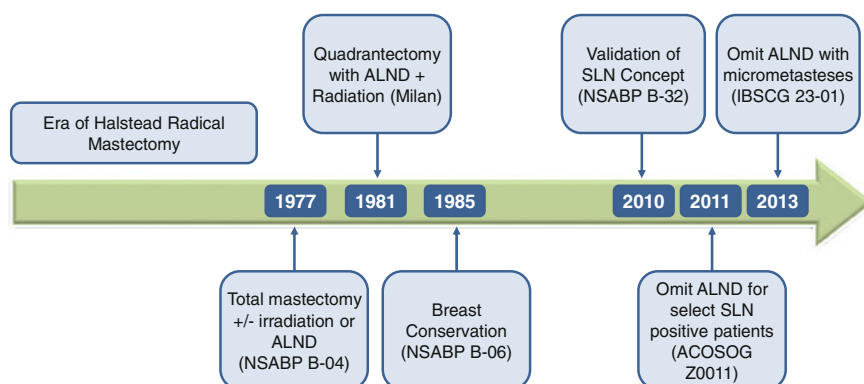


Fig. 1 Impact of efficacy randomized controlled trials on the surgical management of breast cancer (select trials represented)

Project (NSABP)-B06, the clinical trial which defined our current surgical management of breast cancer, women over the age of 70 were excluded. Given that ~40 % of current breast cancer diagnoses occur in women over the age of 70, [4] exclusion criteria such as these have the potential to limit clinicians' ability to apply trial findings to real-life patient populations. Similarly, RCTs require strict adherence to treatment protocols, and may include central auditing of pathology and imaging findings, surgical credentialing, and enhanced patient follow-up; however, many of these components may be altered or omitted as these treatments are implemented in clinical practice, potentially impacting outcomes observed. In contrast to the highly-controlled environment of efficacy trials, effectiveness research provides insight into treatment effects under 'real-world' conditions, which may differ substantially from the trial setting.

There are also a number of factors specific to surgery which make conducting RCTs challenging. In general, the field of surgery has traditionally depended less on RCTs to test new surgical interventions compared to other aspects of medicine, such as clinical drug trials. Consequently, many new surgical techniques (especially those that represent a less invasive or morbid approach) are disseminated into clinical practice prior to any RCT data supporting their efficacy or safety, making it challenging to then generate the supporting data. A pertinent example of this is the SLN biopsy for breast cancer. The SLN biopsy for breast cancer was first described in two small, single-institution studies [5, 6]. In 1999, a RCT began with the intent to validate the SLN biopsy concept [7]. Patients were randomized to SLN biopsy followed by either immediate axillary lymph node dissection (ALND) versus ALND only if the sentinel node was positive. Ultimately, this trial, reported in 2010, demonstrated equivalent overall and disease-free survival as well as regional control with a SLN biopsy [7]. However, in the intervening years between trial initiation and reporting of results, the practice of SLN biopsy became broadly incorporated into standard breast surgery practice, with 59 % of early stage breast cancer patients undergoing SLN biopsy rather than ALND by 2004 [8]. Although the NSABP-B32

trial definitively validates the SLN concept, its practical role was to support the standard of care clinical practice already in place rather than inform practice change.

Additionally, accomplishing randomization in surgical trials can be challenging, as both patients and surgeons dislike the idea of random allocation to a treatment arm. In the era of active patient participation in therapeutic decision-making, patients often resist randomization between surgical treatments, especially if one represents a less invasive therapeutic option. Addressing surgeon biases regarding treatment allocation is equally challenging, as surgeons have their own personal preferences regarding what may be the best treatment option for their patients and a particular familiarity with a given procedure as part of their skill set. Surgeons may be reluctant to recommend enrollment in a clinical trial when they view one of the trial arms more favorably or view the risks of randomization as unacceptably high. Several examples of patient and provider bias can be seen in the execution of prior RCTs in breast cancer. For example:

- American College of Surgeons Oncology Group (ACOSOG) Z0011: This study examined whether ALND is necessary after positive SLN biopsy in women undergoing BCT for invasive breast cancer. Women with positive SLNs were randomized to completion axillary dissection versus observation, and overall survival and local recurrence was determined to be similar between the two groups [9, 10]. Target enrollment was 1,900 patients; however, the study closed early due to lower than expected accrual (<50 % of target) and event rates. This trial began accrual in 1999, at a time when the SLN concept was still being disseminated into wide-spread clinical practice [8]. The timing of trial initiation is likely one factor that influenced the slow accrual, as it may reflect surgeons' reluctance to enroll patients on a trial that avoided an ALND for node positive patients when many were still performing an ALND for even clinically node negative patients. This concept of surgeon bias is further indirectly supported by the low volume axillary disease of patients enrolled in the trial (~40 % with micrometastases), supporting that surgeons selectively enrolled their very low risk patients in the trial [9, 10]. As a result of this clinical trial, women undergoing breast conservation with 1 or 2 positive SLN may be spared a completion ALND. However, the selective accrual of "low-risk" patients to this trial limits the patient populations these findings can be applied to.
- Cancer and Leukemia Group B C9343: This study evaluated patients >70 years of age undergoing BCT to determine whether whole-breast radiation along with tamoxifen improved outcomes compared to tamoxifen alone [11]. Outcomes (recurrence, overall survival) were similar between the groups, and omitting radiation from the adjuvant treatment of women over the age of 70 is now a standard of care option for appropriate women. It is noteworthy that at initiation of the trial, eligibility criteria included T1 or T2 (tumors up to 4 cm) with no restrictions on estrogen receptor (ER) status. However, "in an attempt to broaden participation by physicians concerned about the upper size limit", eligibility criteria was changed to limit tumor size to 2 cm and require ER status to be positive or unknown. Following this change, accrual was rapidly completed. Of note, at accrual completion, only 14 of 636 women had T2 tumors, and only ten

were ER negative [11]. As a result of this clinical trial, women over the age of 70 may consider omitting radiation from their breast conservation treatment plan, although the applicability of this study’s findings is limited to a small subset of the older breast cancer patient population due to its strict inclusion criteria.

These examples highlight the challenges associated with randomization in surgical trials, as well as how surgeon bias can affect trial accrual and even lead to early trial closure. Ultimately, these issues will impact generalizability of the clinical trial to the real world setting.

3 Breast Cancer-Specific Limitations to Efficacy Trials

In addition to the general challenges associated with conducting RCTs, there are a number of unique characteristics associated with breast cancer which make some aspects of care difficult to assess with a RCT (Table 1). These largely reflect our

Table 1 Limitations of efficacy randomized controlled trials in breast cancer and possible solutions provided by comparative effectiveness research

| | Challenges to performing RCT in breast cancer | Use of CER to overcome challenges |
|--|--|---|
| Improved outcomes (survival, recurrence) | Large number of patients required to identify small differences in oncologic outcomes | Retrospective evaluation of large data sets (i.e. administrative data, etc.) |
| | Extended follow-up period to assess delayed outcomes | Meta-analysis to evaluate pooled data |
| | Often prohibitively time and financially intensive, given favorable overall prognosis | Decision-modeling to evaluate theoretical outcomes associated with different options |
| | Discrepancy between outcomes in clinical trial and real life | Pragmatic clinical trials to evaluate real life outcomes with |
| | Improved outcomes may increase relative importance of other patient-centered outcomes (see below) as surrogate endpoints | incorporation of patient-centered outcomes |
| Patient preferences | Breast cancer management especially preference-sensitive | Retrospective evaluation of large data (avoids need for randomization but requires selection bias controls) |
| | Patients may resist randomization if not aligned with their values | Use of qualitative research to explore patient values |
| | Some questions not amenable to randomization | Development of validated decision aids |
| Patient-centered outcomes | Few validated tools for objective measurement of outcomes | Expanded research to develop tools assessing outcomes valued by stakeholders |
| | Subjective and objective measures may not correlate | Qualitative research methods to explore stakeholder values |

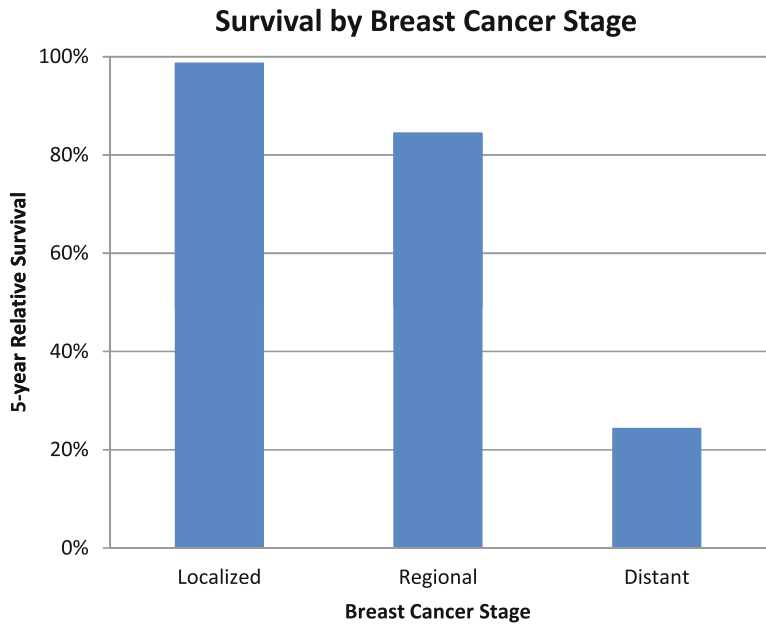


Fig. 2 5-Year Breast Cancer Survival by Cancer Stage [4]

success in treating breast cancer (with an associated improved survival) and the increasing role patients and their preferences play in treatment decision-making.

Implications of Prolonged Survival: With improvements in cancer detection and treatment, the prognosis for breast cancer patients has markedly improved in the past 20 years. The 3-year survival for the 3 million breast cancer survivors currently living in the United States exceeds 97 % for localized (node negative) and 84 % for regional (node positive) disease (Fig. 2) [4]. The increased overall survival and decreased local recurrence associated with modern breast cancer treatment represents a challenge in conducting efficacy RCTs, as predicted differences between treatment groups will be small and require an extended period of follow-up to identify. Conducting such trials would therefore require large patient cohorts to have adequate power which will be prohibitively expensive and time-intensive, and may not yield a meaningful clinical outcome.

One option to address this challenge is to limit inclusion criteria for clinical trials to select “higher-risk” sub-groups for whom differences may be more easily observed. However, such inclusion criteria may increase the difficulty in patient accrual, and would not represent a feasible method for studying processes with high cure rates like DCIS.

Patient Preference: When compared to other cancers, decision-making surrounding breast cancer management is especially preference-sensitive (decisions regarding mastectomy versus breast conservation, reconstruction choices, etc.). These preferences may also determine how patients perceive and ultimately decide

to participate in, a clinic trial. Investigators must therefore address this in their trial design to ensure adequate trial accrual. For example, NSABP-06 randomized women between one of the three treatment arms: mastectomy, segmental mastectomy followed by breast irradiation, or segmental mastectomy alone. These treatment arms represent therapies with relevant differences in patient-centered outcomes including quality of life and body image. In recognition of the challenges to randomly assigning women to one of these very different arms, investigators designed the trial using a “pre-randomization” technique. After assessing women for eligibility this study, patients were pre-assigned to one of the treatment groups. Patients were then approached for participation and disclosure of their pre-randomization arm was included in the consent process. Only patients who accepted their pre-assigned therapy and provided informed consent were enrolled in the trial. A total of 2,024 women were randomized to the three treatment arms. Despite these measures, the assigned treatment was still refused by 175 patients, with 78 refusing mastectomy, 55 refusing segmental mastectomy plus breast irradiation, and 41 refusing segmental mastectomy alone [12]. Overall, however, this “pre-randomization” design allowed patients to consider their personal preferences for treatment when deciding whether to participate in the trial and allowed successful completion of the trial, which defines our current standard of care for breast cancer surgery.

In addition to representing a challenge to trial accrual, patient preference limits to some degree what types of questions can be answered in efficacy trials, as randomization for many questions may be either unethical or not feasible. One pertinent example is examining outcomes of risk-reducing surgery for women at elevated risk of developing breast cancer (i.e. *BRCA1* and *BRCA2* mutation carriers). To date, there is no level 1 evidence supporting a survival benefit to risk-reducing surgery, and the necessary study is unlikely to ever occur given the ethics associated with randomizing high-risk women in such a preference-laden scenario. Other examples of clinical questions unlikely to be answered through efficacy RCTs include consideration of the role of contralateral mastectomy for women with a new cancer diagnosis and outcomes after different types of post-mastectomy reconstructive procedures.

Studying Patient-Centered Outcomes: With the improvement in recurrence and survival observed in breast cancer, increasing emphasis has been placed on alternative patient-centered outcomes such as range of motion, quality of life, sexual function, cosmesis, and patient satisfaction. These outcomes can be negatively impacted by the breast cancer treatment administered, and are highly valued by breast cancer survivors. Unfortunately, it can be challenging to measure these outcomes as appropriate and sensitive tools are not always available. Additionally, the relative importance of many of these outcomes may vary based on the individual patient, and objective and subjective measures of the same outcome may not correlate. For example, in a prospective study of lymphedema in women who underwent SLN biopsy or an ALND, significant differences were observed in the rates of patient-reported (subjective) and objectively measured lymphedema [13]. Further, many survivors with objectively measured changes in limb volume did not report having clinical symptoms of lymphedema. This example highlights some of

the challenges associated with evaluating patient-centered outcomes and even defining what outcomes should be measured.

Further, understanding patient satisfaction in relation to surgical decision-making, reconstruction, and cosmesis is in its infancy. Although reconstruction plays a key role in patient satisfaction for their surgical breast cancer treatment, it has no effect on cancer recurrence or survival and is therefore rarely reported in RCTs. Assessment of cosmetic outcome is extremely challenging and difficult to quantify, although robustly validated measurement tools are becoming more readily available [14]. Patients' assessment of their cosmetic outcome is heavily impacted by pre-operative expectations and their overall satisfaction with their cancer care, resulting in possible discordance between objective and subjective measures. Finally, there are notably wide regional, socio-economic, and demographic variations in rates of breast reconstruction after mastectomy that are poorly understood. Although these variations are likely multi-factorial, patient preferences and values play an important role in patient decision-making for reconstruction and the differences in priorities between different populations represent an additional challenge in assessing these and similar outcomes.

4 Breast Cancer Clinical Questions Amenable to Comparative Effectiveness Research

In day-to-day practice, physicians routinely encounter clinical questions about breast cancer care which have not been satisfactorily addressed with RCT data and are unlikely to be ever addressed in this manner. However, many of these questions may be appropriate to examine using CER methodologies. Summarized below are several key clinical questions in breast cancer which do not currently have RCT-based evidence available to guide decision-making. We will discuss why these particular questions are important to address as we strive to improve the quality of care we provide breast cancer patients, examine why they are not amenable to study using typical efficacy trials, and explore how these questions may be approached from a CER perspective.

Breast Cancer Screening: Significant controversy surrounds the recent recommendation from the United States Preventive Services Task Force (USPSTF) that routine screening mammography for average-risk women begin at age 50 [15]. The rationale for this recommendation stems from the lower rate of breast cancer and the higher rate of false positive results in women under the age of 50. Significant controversy exists, however, because mammography represents a low-cost, non-invasive screening tool. In addition, recommendations represent those for the average woman, and specific guidance is not providing regarding how to adapt these guidelines for subgroups of women at increased risk of breast cancer (i.e. those with a strong family history). While several RCTs have been completed comparing mammography to no intervention [16] and found a statistically significant mortality benefit, these studies were not powered to evaluate the benefits of

mammography for patients based on individual risk factors. Given our relatively limited ability to identify younger women at high risk of breast cancer who may benefit from initiation of earlier screening, critics of the new guidelines feel that screening of the entire population is warranted to minimize the incidence of missed cancers. Given the wide-spread acceptance by both clinicians and women of the importance of mammography in breast cancer screening, the question of whether or not to screen women under the age of 50 with mammography will never be addressed in a RCT, making it appropriate for a comparative effectiveness approach. This question could be addressed through a number of mechanisms. One option would be to perform observational or retrospective studies using existing data sources, such as mammography registries. These often include more detailed information on individual risk factors than is available through cancer registry data (such as SEER) making these registries a rich data source. Systematic reviews represent one alternative approach. As an example, a recent meta-analysis of more than 60 studies sought to identify risk factors associated with increased risk of breast cancer in women ages 40–49 [15]. Although these systematic reviews are limited to data available in the studies included, this review was able to identify risk factors associated with 1.0–1.5, 1.5–2.0, or greater than 2.0- fold increased risk for invasive carcinoma which could then be used to guide screening decisions for younger women. Modeling techniques such as decision-analysis or cost-effectiveness analysis are another feasible approach. In a study by Schousboe et al. [17] mammography was found to be beneficial both in terms of quality-adjusted life years and cost-effectiveness for younger women who had either dense breasts or both a family history of breast cancer and personal history of breast biopsy. This study utilized data from the SEER program as well as the Breast Cancer Surveillance Consortium. These types of study design represent the most practical way to assess the impacts of discrete risk factors on breast cancer risk and subsequent potential benefit of screening mammography, and may guide the development of more individualized mammography screening recommendations.

Management of DCIS: With improved imaging techniques, diagnosis of DCIS has increased throughout the past two decades. While DCIS represents a pre-cancerous lesion, there is a range of histology and cell biology within this category and some risk of eventual conversion to invasive carcinoma. Unfortunately, data is scant on long-term outcomes for the various grades of DCIS and we are currently unable to predict which patients, if untreated, will progress to invasive cancer and which patients have a clinically insignificant lesion. Patients are therefore generally treated as a homogenous group with local surgical control, often combined with radiation and risk-reducing endocrine therapy. Given the excellent overall prognosis of patients with DCIS, the challenge lies in identifying not only statistically but also clinically significant differences in outcomes between various treatment approaches, applying these approaches to different subgroups of patients, and then incorporating patients' personal values into subsequent treatment decision-making. For example, although radiation after BCT decreases the risk of local recurrence, it has a limited impact on overall survival. Further, it may result in poorer cosmetic outcomes, increase the risk of lymphedema, limit future treatment options should

cancer recur, and represents a significant time commitment on the part of the patient (with potential financial repercussions if radiation therapy appointments interfere with her ability to work). These patient-centered outcomes, although they factor into patient decision-making, are difficult to incorporate into traditional efficacy trial designs and make this question especially amenable to CER. The issue of management of DCIS has been addressed in a number of CER studies. A recent publication by Soeteman et al. [18] created a disease simulation model for six possible treatments of DCIS, utilizing outcome data from well-executed RCTs. Based on the grade of DCIS (low, intermediate, high) and simulated age at the time of diagnosis, the team identified the degree of benefit conferred by each therapeutic option in terms of breast preservation and disease-free, invasive disease-free and overall survival for a hypothetical patient. They found that overall, the survival benefits associated with different therapeutic approaches to management of DCIS were comparable, with the maximum difference in survival between therapeutic options estimated to be 12 months. Given that this could be perceived as a clinically “less significant” difference, the authors suggested therapy for DCIS could be tailored based on patient values, including preferences for breast preservation and/or their wish to avoid a recurrence.

A second example of CER and DCIS utilized SEER-Medicare data to evaluate outcomes for older women who underwent lumpectomy with or without radiation [19]. The team identified more than 3,400 women ≥ 65 years of age who underwent lumpectomy with or without radiation therapy for DCIS. Additional data were collected to evaluate high-risk features (age 66–69 years, tumor ≥ 2.5 cm, comedo- and/or high-grade histology). Patients were then followed to determine whether they experienced an ipsilateral recurrence and/or underwent ipsilateral mastectomy. Researchers determined that radiotherapy was associated with a significant reduction in ipsilateral recurrence and subsequent ipsilateral mastectomy, especially for those patients with high-risk features. This data has high utility in providing clinicians with information which can guide shared-decision-making conversations with older patients regarding the management of their DCIS.

Margin Status: BCT is a standard of care option for surgical management of breast cancer, and the importance of obtaining negative margins to minimize local recurrence is clear. However, controversy remains surrounding what constitutes an “adequate” surgical margin. Current NCCN guidelines indicate that margins of 1 cm are always adequate, while margins ≤ 1 mm (no ink on tumor) are not, [20] but there is no consensus on any margin between these values for either DCIS or invasive breast cancer. These variable definitions of what constitutes negative margins may place patients at increased risk of local recurrence or alternatively lead to unnecessary re-excisions. Although this question could be addressed through a standard efficacy trial, the number of patients required and the duration of follow-up necessary to assess local recurrence as an outcome makes such trials unfeasible.

A number of options exist, however, to address this question through CER using existing data. One option is a meta-analysis of published data. As an example, a recent study assessed patients with DCIS treated with lumpectomy and radiation found increased rates of ipsilateral recurrence with margins < 2 mm compared to

margins >2 mm; however, there were no significant differences in recurrence for patients with margins of 2–5 mm or >5 mm [21]. Retrospective analyses of prospectively collected data (i.e. data collected systematically for a different initial purpose such as a clinical trial) would be an alternative means of address this question and has the potential to have a significant impact on how breast cancer surgery is currently practiced.

Management of the Positive SLN: After establishment of SLN biopsy as standard of care for staging the axilla, thousands of women with node negative cancer have been spared ALND. With the publication of two recent RCTs, there is now data to support omitting ALND in some women even with positive axillary nodes. As discussed earlier, the ACOSOG Z0011 trial examined women undergoing breast conserving surgery and SLN biopsy for invasive breast cancer, and found the use of SLN biopsy alone to be non-inferior to ALND in terms of survival, for eligible women [9, 10]. Similarly, the recently reported European Organization for Research and treatment of Cancer After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial evaluated outcomes for women with T1/T2 breast cancer and positive SLN's; women undergoing either mastectomy or BCT were included, although 82 % underwent BCT (making the study population very similar to that observed in ACOSOG Z0011) [22]. Women were randomized to either ALND or axillary radiotherapy to levels I-II, with optional radiotherapy to level III. Although the study was underpowered to evaluate its primary endpoint, axillary recurrence, no clinically meaningful difference between the groups was observed (0.54 % after ALND versus 1.03 % after axillary radiotherapy).

Although both of these studies were underpowered, they provide strong supporting evidence that not all women with a positive SLN biopsy require a completion ALND (Table 2). However, these findings are largely applicable only to women undergoing BCT, with AMAROS providing only limited data on women undergoing mastectomy. Given the challenges in completing both of these trials, it is unlikely that further RCT of SLN positive women undergoing mastectomy will be initiated in the near future. This represents a unique opportunity to examine this question using CER, likely through existing administrative and clinical databases (while acknowledging some of the selection biases reflected in these data sources).

Survivorship and Surveillance: Since the publication of the Institute of Medicine Report, "From Cancer Patient to Cancer Survivor: Lost in Transition," [23] the focus on the quality of survivorship for cancer patients has increased. One area of focus which has been increasingly recognized by stakeholders as a priority is follow-up surveillance, with the recognition that little data exists to support the follow-up recommendations that currently exist.

Given the high overall survival and uncertainty surrounding the true clinical efficacy of a clinical follow-up exam, it is unclear which breast cancer survivors truly need prolonged follow-up with an oncologist, and when, if ever, primary care providers should assume a primary role in surveillance. Reducing unnecessary clinic visits represents a potential benefit to patients as they transition from active treatment back to their activities of daily living, and a timely transition would alleviate the burden of routine surveillance on specialty providers. However, it is

Table 2 Review of two trials evaluating management of the axilla with a positive sentinel lymph node

| Trial | Patient population | Trial arms | Patient accrual | Endpoints | Findings | Limitations to generalizability |
|--------------|---|---|-----------------|--|---|---|
| ACOSOG Z0011 | Adult women with T1/T2 tumors undergoing BCT, with 1–2 positive SLN | Completion ALND versus no further therapy | 901 pts | Local and regional recurrence | Local recurrence: 1.8 % in SLN biopsy arm versus 3.6 % in ALND arm | Study closed early due to poor accrual (<50 % target) and was underpowered |
| | | | | | Regional recurrence: 0.9 % in SLN biopsy arm versus 0.5 % in ALND arm | Included patients had small tumors and low volume axillary disease |
| | | | | | | Only included patients undergoing BCT |
| AMAROS | Adult women with T1/T2 tumors undergoing either mastectomy or BCT with a positive SLN | Axillary radiation versus ALND | 1,425 pts | Axillary recurrence, overall- and disease-free survival, quality of life | Axillary recurrence: 0.54 % in ALND arm versus 1.03 % in axillary radiation | All received whole breast radiation (no additional planned axillary tangents) |
| | | | | | | Study was underpowered |
| | | | | | | Limited data on mastectomy pts (82 % underwent BCT) |
| | | | | | | Included patients had small tumors and low volume axillary disease |

also likely that different patient populations (based on age, tumor characteristics, and treatment received) may benefit differently from clinical follow-up, adding to the challenge of refining current follow-up. As a result of these factors, examining the impact of different surveillance regimens through traditional RCTs is difficult.

Further, the Institute of Medicine has recommended that all cancer patients receive at the completion of therapy a survivorship care plan [23]. This plan provides details about the patient's cancer history (diagnosis, surgery, and treatment), outlines details of ongoing surveillance (frequency of visits, labs, and imaging, and responsible health care provider), and provides information about support for possible side effects of therapy and general health promotion strategies. However, no data exist to date examining the true impact of care plans (positive or negative) on patients or providers.

CER represents a viable method of addressing these types of questions to improve the quality of comprehensive survivorship care. Administrative databases, such as SEER Medicare, with their available longitudinal data, allow current patterns of care studies to be performed, providing insight into how different patient factors may influence follow-up visits or receipt of imaging [24]. However, SEER-Medicare is limited by the composition of its population (patients over the age of 65), making generalizability of these findings to the greater breast cancer patient population difficult. Further, administrative data sources such as SEER-Medicare cannot provide insight into the decision-making underlying the patterns of care observed.

Other techniques, such as qualitative research methods (focus groups, interviews), may be necessary to understand the preferences of key stakeholders (patients, primary care physicians, medical, surgical, and radiation oncologists) for follow-up care and how these preferences influence follow-up care delivered and received. Findings from such mixed-methods studies will complement the quantitative data and will provide critical insight into how stakeholders perceive follow-up. Cost-effectiveness studies, with a focus on both the financial and "person" costs of follow-up, will also likely play a substantial role in refining current follow-up. These approaches are also the optimal means of evaluating the relative impact of current survivorship care plans on patient care.

Finally, comparison of various surveillance protocols will necessitate creative approaches to any future efficacy trials. Randomization of individual patients is impractical and would create significant hardship for participating centers. A clustered randomized controlled trial, in which groups of patients rather than individual patients are randomized, represents one possible approach that would simplify the study design but still allow some degree of randomization.

Disparities in Breast Cancer: Significant disparity exists in many aspects of breast cancer. When examined along racial or socio-economic lines, rates of breast cancer screening, diagnosis, treatment, reconstruction after mastectomy, and mortality vary widely. For example, in a recent literature review examining ethnic differences in breast cancer survival, Maskarinec et al. [25] found that compared to white women, African-American women had a hazard ratio of breast cancer-specific mortality of 1.2–1.3, while Latinas had a breast cancer mortality risk of 1.1. Asian-Americans as a whole have significant variability by sub-group, although

women of Japanese descent have a survival advantage of about 20 % compared to Caucasians [25]. These authors also found that disparities were smaller but persistent in studies that controlled for confounding variables such as access to health care, obesity, and co-morbidities. They note that many of these confounders are closely tied to socio-economic status and may contribute to prognosis to multiple ways.

Given the under-representation of these populations in clinical trials, our efficacy RCTs can provide only limited insight into the factors underlying these disparities. In contrast, CER represents an opportunity to study these populations in “real world” settings, focusing on how geographic, socioeconomic, and cultural/social constructs impact treatment received and subsequent outcomes. Use of administrative databases combined with other research techniques such as qualitative interviews will be crucial in further investigative efforts.

5 Future Steps

CER for breast cancer represents a unique opportunity to address many of the pertinent questions that need to be answered to further improve the quality of care we provide to breast cancer survivors, while balancing the challenges associated with traditional efficacy trials. However, many of these questions remains difficult to address, and success will require the development of additional infrastructure to support CER efforts, creation of new data sources, and use of new research methodologies.

Fortunately, several new initiatives are in progress which will begin to address current deficits in data collection and coordination. One such initiative is the reorganization of the National Cancer Institute (NCI) trials network to include cancer care delivery research, which includes CER. Originally developed to facilitate efficacy RCTs, the NCI is interested in developing this infrastructure to support large research initiative. Cancer cooperative groups have accumulated data on patient demographics, treatment details, and longitudinal outcomes. Some of these outcomes of interest, including toxicity and cancer recurrence, are difficult to track from other currently available data sources (such as administrative data) and therefore represent a unique potential resource for cancer CER. This potential was recognized by the Alliance for Clinical Trials in Oncology, a merger of the former North Central Cancer Treatment Group, American College of Surgeons Oncology Group, and Cancer and Leukemia Group B. The American College of Surgeons Clinical Research Program (ACS-CRP), a joint initiative of the Alliance and The American College of Surgeons Cancer Program, was created with the goal of utilizing the Alliance’s infrastructure to expand health services, patient-centered research, and CER. This will be executed through a partnership with the Commission on Cancer of the American College of Surgeons, which includes a national network of 1,500 hospitals involved in quality cancer care and research.

Another major initiative is the development of the Oncology NSQIP National Cancer Institute Center Consortium, composed of 51 hospitals accredited by the National Cancer Institute that are currently participating in NSQIP. Like the Alliance programs, this consortium was developed with the recognition of the importance of CER in addressing pertinent oncology questions and focus on sharing and comparison of oncology-specific data to improve outcomes; improvement and expansion of risk-adjustment, process measures, and short-term outcomes utilized by NSQIP; and providing infrastructure and resources for prospective and retrospective CER.

These coordinated efforts greatly expand the resources available to answer many important breast cancer-related questions. Additionally, the framework of CER, which encourages use of alternative research methodologies beyond traditional efficacy RCTs, is critical. These research methods and their potential contributions to clinical care are illustrated throughout this chapter. Methods such as cluster RCTs, decision modeling, meta-analyses, qualitative studies, and novel “big data” sources will allow us to understand key clinical problems when efficacy RCTs are impractical or impossible to conduct and, importantly, will allow the incorporation of patient-centered outcomes, an increasingly recognized focus. The clinician caring for breast cancer patients must be familiar with these approaches to stay current with the literature, and as we move into the twenty-first century, CER will play an expanded role in answering key clinical questions.

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