Landmark Trials in Oncology

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ISBN 978-3-030-14404-3 ISBN 978-3-030-14405-0 (eBook)
https://doi.org/10.1007/978-3-030-14405-0

Library of Congress Control Number: 2019936578

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The well-designed clinical trial is essential to the field of medicine. While doing my residency training in radiation oncology several years ago at Memorial Sloan Kettering Cancer Center, there was a daily morning conference during which trainees were expected to have the important details of landmark clinical trials committed to memory. Having practiced radiation oncology for the past 15 years, I have seen the tremendous impact that well-designed clinical trials have made on the field of oncology. Both the initial respect for well-designed clinical trials engendered through rigorous training and the first-hand experience of seeing how clinical trials improve the lives of my patients have created in me a deep respect for the well-designed clinical study.

This book summarizes key findings from approximately 250 landmark clinical trials in oncology. The author makes no claims toward completeness. This selection of trials reflects the knowledge base, clinical and intellectual interests and training of the author who is a radiation oncologist. However, precisely because oncology is a multidisciplinary endeavor, these studies should be of interest to radiation oncologists, surgeons, medical oncologists, and other physicians interested in learning more about the trials that have impacted oncology. The reader is encouraged to refer to the full manuscript of these trials. The material is for educational purposes only, serving as a starting point for deeper and more nuanced inquiry.

I would like to thank my colleagues who reviewed aspects of this book and provided suggestions for improvement. Most of all, I would like to thank the investigators who design, implement, and report well-designed clinical trials. Their contributions are invaluable. This book seeks to honor their work.

Chicago, IL, USA Santosh Yajnik, M.D.

Contents

1 Introduction to Landmark Trials in Oncology

The well-designed clinical trial is essential to the field of medicine. Such trials allow us to know things with statistical certainty, where in the absence of such trials, we are left with only guess work. As stated by the Lasker Prize winning surgeon and researcher Dr. Bernard Fisher, "The clinician, no matter how venerable, must accept the fact that experience, voluminous as it might be, cannot be employed as a sensitive indicator of scientific validity."

Prospective clinical studies to develop new treatments progress through phases of trial design. Phase 1 trials are designed to assess the pharmacokinetics, tolerability, and safety of new agents. These trials are often conducted in heavily pretreated patients who may have refractory disease, and the number of patients accrued to phase 1 trials is usually small. Select therapies that graduate from phase 1 are moved to phase 2 trials, which are designed to assess therapeutic activity in a better-defined disease population. Phase 2 trials evaluate efficacy, and some include a dose-finding component. If treatments are found to be successful in the phase 2 setting, the gold standard is to compare the experimental treatment against an existing standard of care in a prospective, randomized, phase 3 trial (Fig. 1.1). Phase 3 trials typically have large numbers of patients. If results in the phase 3 setting indicate that a new treatment demonstrates improved efficacy or tolerability, then a new approach to management may emerge.

The process of bringing a new drug from the basic science bench into clinical practice can take longer than 10 years. There are hundreds of novel agents that are currently in clinical trials for the treatment of cancer. Newer methods of trial design are trying to more efficiently bring these medicines to patients. One example is the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial, which uses a multigroup, multistage design to study the addition of newer therapies for men with locally advanced or metastatic prostate cancer who are starting androgen deprivation therapy [1]. The STAMPEDE trial design has allowed investigators to study multiple agents in the setting of a single prospective trial. Up to 10 different primary questions are expected to be addressed over 15-years via this trial.

Another example of novel trial design is the KEYNOTE-001 trial. KEYNOTE-001 was the first phase 1 single-arm trial that was subsequently adapted, through multiple amendments, to enroll 1235 patients and address the role of pembrolizumab for patients with melanoma and non-small cell lung cancer [2]. KEYNOTE-001 did not restrict itself to one phase of trial design or one specific clinical question in a single disease site. Instead, KEYNOTE-001 contained multiple nested phase 2 type studies and six randomized trials using multiple expansion cohorts. This allowed multiple clinical questions to be addressed and led to expedited approval of

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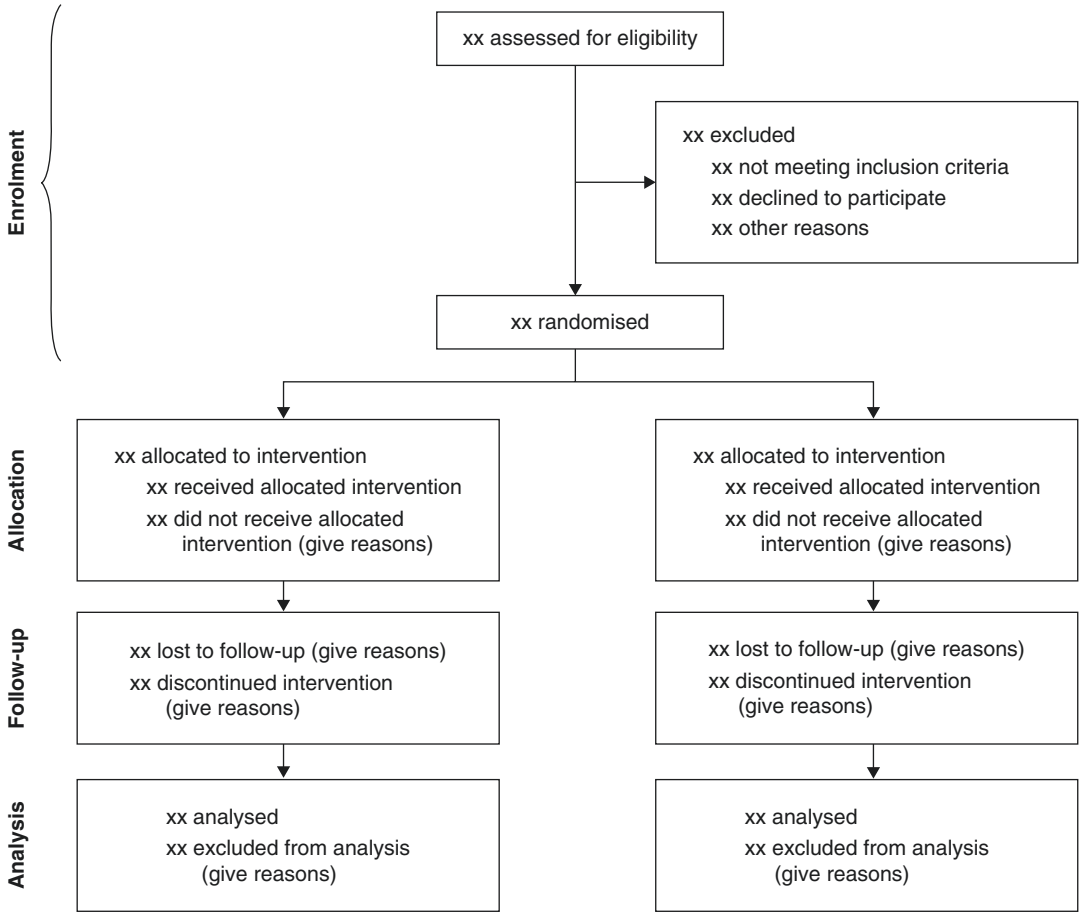

Fig. 1.1 Flow diagram through the phases of a parallel randomized trial of two groups. (Figure from Schulz et al. for the CONSORT Group. Lancet, 2010 with permission)

pembrolizumab for multiple indications. Pembrolizumab received its first FDA approval for use in patients with melanoma about 4 years after its designation as an investigational new drug. Thus, the KEYNOTE-001 trial serves as an example of a novel way that breakthrough drugs can more efficiently be studied on the pathway to regulatory approval. There are currently hundreds of clinical trials evaluating pembrolizumab across tens of different primary cancer indications.

It is essential that we pay close attention to the quality and potential biases in the design and reporting of clinical trials. For example, the funding for clinical trials has changed since the 1980s with approximately 70% of the funding for drug trials coming from the pharmaceutical industry [3]. How does a change in funding source impact study design and reporting and how are we to appropriately interpret the results of these trials?

Booth et al. reviewed randomized clinical trials in breast, non-small cell lung, and colorectal cancer performed between 1974 and 2004 to evaluate trends in methodology and reporting, funding, and the interpretation of outcomes. They evaluated 321 articles that included 171,161 cumulative randomized patients. Booth et al. found a shift from clinical response rate as the primary endpoint (down from 54% to 14%) to the time-to-event endpoints (up from 39% to 78%). They found a shift from government funding (down from 60% to 31%) to industry funding (up from 4% to 57%). They also found that for-profit organization-sponsored studies

were more likely to be conducted in the setting of metastatic disease and had larger sample sizes. Booth et al. found that one-third of randomized clinical trials published between 1995 and 2004 did not explicitly identify the primary endpoint. The proportion of studies for which investigators strongly endorsed the experimental arm had increased from 31% to 49% over the 30-year study period ($P = 0.017$). The strongest predictor for the study authors endorsing the new therapies was statistically significant outcome, but they also found that industry sponsorship was an independent predictor for studies being reported as a positive trial.

Based on increasing concern that researchers may be doing a poor job in both designing and reporting results of randomized controlled trial, the scientific community has made significant progress in monitoring the quality of clinical trials. Some of the flaws in conducting and reporting trials may be the result of investigator bias. The Consolidated Standards of Reporting Trials (CONSORT) guidelines have been developed to standardize and improve the quality of reporting of clinical trials [4].

The membership of the CONSORT group is comprised of clinical trialists, statisticians, epidemiologists, and editors. The CONSORT group strives to be dynamic and evolve with the literature. There are over 700 studies that form the CONSORT database and provide the evidence for the CONSORT guidelines. The International Committee of Medical Journal Editors endorsed CONSORT, and the Council of Science Editors and World Association of Medical Editors officially support CONSORT. CONSORT has been supported by over 400 journals published around the world. One goal of the CONSORT group is to standardize reporting of outcomes, including a 22-item checklist to facilitate uniform publication of results (Table 1.1). The CONSORT group believes that the proper design and implementation of clinical trials is essential to accurate reporting. They believe that an optimized reporting format would expose weaknesses in the design and conduct of clinical trials, thereby driving improvement in the quality of research. The CONSORT Group stated, "with wide adoption of CONSORT by journals and editorial groups, most authors should have to report transparently all important aspects of their trial. The ensuing scrutiny rewards well conducted trials and penalizes poorly conducted trials."

As a radiation oncologist, the well-designed clinical trial is essential to my profession. During residency training at Memorial Sloan Kettering Cancer Center, we had a daily morning conference during which trainees were expected to have the important details of landmark clinical trials committed to memory. Having practiced radiation oncology for the past 15 years, I have seen the tremendous impact that well-designed clinical trials have made on the field of oncology. Both the initial respect for well-designed clinical trials engendered through rigorous training and the first-hand experience of seeing how clinical trials improve the lives of my patients have created in me a deep respect for the well-designed clinical study.

This book contains a summary of key findings from a selection of approximately 250 landmark clinical trials dealing with several common malignancies. The format of each chapter is standardized. In order for the reader to know what material is covered in each chapter, a detailed abstract provided at the beginning lists the topics and trials that are discussed. Each chapter contains an introduction, a description of the methodology and key findings of the selected trials, a list of pending or future trials, and bibliography. In situations where multiple prospective randomized trials may have addressed a given topic (e.g., postmastectomy radiation therapy for breast cancer or chemoradiotherapy for definitive management of cervical cancer), a relevant meta-analysis has been selected to represent this area of knowledge. While most trials are prospective, in select situations, a retrospective study is included.

Acronyms have been used to represent the cooperative groups such as the Cancer and Leukemia Group B (CALGB), Radiation Therapy Oncology Group (RTOG), and Gynecologic Oncology Group (GOG). Since staging has evolved over the past several decades, the staging referred to in this book for each clinical trial refers to the staging system in place at the time

Table 1.1 Checklist of information to include when reporting a randomized trial per CONSORT 2010

Section/topic	Item number	Checklist item	Reported on page number
Title and abstract			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts[21,31])	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	
	13b	For each group, losses and exclusions after randomization, together with reasons	

Table 1.1 (continued)

Section/topic	Item number	Checklist item	Reported on page number
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by originally assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% CI)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms[28])	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

Table from Schulz et al. for the CONSORT Group. Lancet, 2010 with permission
*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration[13] for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials,[11] noninferiority and equivalence trials,[12] nonpharmacological treatments,[32] herbal interventions,[33] and pragmatic trials.[34] Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist see http://www.consort-statement.org

the research was conducted and is taken from the manuscript being referenced.

This book has several limitations. One of the foremost limitations is that the format of a single-authored book does not allow for completeness. There are thousands of clinical trials that could have been included. Therefore, no claim is made toward completeness. This selection of trials reflects the knowledge base, clinical and intellectual interests, and training of the author who is a radiation oncologist. If you are a medical oncologist or surgeon, you would certainly have chosen different trials and written a different book. However, precisely because oncology is a multidisciplinary endeavor, these studies should be of interest to radiation oncologists, surgeons, medical oncologists, and other physicians interested in learning more about the landmark trials that have impacted oncology. Another important limitation is that a summary of key findings from a study does not equate in thoroughness to the entire manuscript. Therefore, I hope that this work inspires readers to refer to the full manuscript of these trials for a deeper understanding.

The information contained in this book is for educational purposes only and is not management

advice. I would like to thank my colleagues who reviewed aspects of this book and provided suggestions for improvement. Most of all, I would like to thank the investigators who design, implement, and report well-designed clinical trials. Their contributions are invaluable. This book seeks to honor their work.

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Landmark Trials in Breast Cancer

2

2.1 Introduction

Prospective, randomized trials have played an essential role in the improvement in care for patients with breast cancer. Even when treatment in the past has been suboptimal, well-designed clinical trials have allowed us to correct course and continue to make progress in improving outcomes for our patients. There was an almost century long period during which hundreds of thousands of women underwent Halsted radical mastectomy because it was believed, without randomized or high-level evidence to support such a claim, that simply operating more aggressively would produce the elusive increase in cure rates. However, several well executed prospective, randomized clinical trials disproved this dogma that more surgery was always better, and as a result of landmark clinical trials, the Halsted radical mastectomy is rarely performed today.

It took a surgeon working out of the University of Pittsburgh named Dr. Bernard Fisher, as head of the National Surgical Adjuvant Breast and Bowel Project (NSABP), to spearhead studies such as NSABP B-04 and NSABP B-06 that finally convinced the oncology profession that more aggressive surgery was not always the best treatment course for breast cancer. These landmark trials established that the Halsted radical mastectomy was no better than total mastectomy (B-04) and that breast conservation therapy consisting of lumpectomy followed by radiation therapy (B-06) could be offered safely to properly selected patients.

Other trials quickly followed that also served to lessen the burden of surgery in properly chosen patients with breast cancer. For example, the landmark NSABP B-32 trial demonstrated that sentinel lymph node biopsy, which had been introduced in the 1980s for the management of melanoma, could be safely performed in node negative patients with breast cancer and potentially spare the pain, edema, and range of motion and sensory deficits often experienced by patients who underwent full axillary lymph node dissection.

The landmark Cancer and Leukemia Group B (CALGB) 9343 study was conducted in a population of women aged 70 years and over with more favorable estrogen receptor-positive breast cancer resected with negative margins. This trial demonstrated that while such older patients with early-stage and favorable disease experienced a modest local control disadvantage with the elimination of post-lumpectomy radiation therapy, there was no overall survival disadvantage when radiation therapy was eliminated from adjuvant management following breast-conserving surgery, as long as patients agreed to treatment with 5 years of endocrine therapy.

The role of adjuvant radiation therapy for breast cancer continues to evolve, and its uses are being better defined. Multiple studies have evaluated which population of patients benefit most from

S. Yajnik, *Landmark Trials in Oncology*, https://doi.org/10.1007/978-3-030-14405-0_2

adjuvant radiation therapy. For example, multiple randomized trials and a meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated a survival advantage for postmastectomy radiation therapy in lymph node-positive patients, even when one to three lymph nodes are involved with cancer.

The landmark AMAROS trial demonstrated the benefit of adding regional nodal irradiation in sentinel node-positive patients who did not undergo a completion axillary dissection. Similarly, the MA-20 trial helped better define which population of women with breast cancer benefit from the addition of regional nodal irradiation.

Clinical trials have established which systemic therapies provide a survival advantage in breast cancer. A regrettable misstep in the management of breast cancer occurred when thousands of women around the world underwent high-dose chemotherapy with stem cell transplant without clear evidence to support its use. Once again, it was randomized clinical trials such as the Southwest Oncology Group/Intergroup Study 9623 that helped to demonstrate that there was no survival advantage to using stem cell transplant over more standard chemotherapy in women with breast cancer.

The Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741 and several other trials have helped to demonstrate the appropriate sequencing of systemic therapy and benefits of dose density when using adjuvant chemotherapy in appropriately selected patients. A meta-analysis by Mauri et al. compared the same systemic therapy regimen delivered either in neoadjuvant or adjuvant fashion as part of definitive management of localized breast cancer.

Selected landmark clinical trials are presented that helped establish the benefit of endocrine therapy and targeted therapies against the Her2Neu receptor in eligible patients. Moreover, the paradigm changing NSABP P-01 study is discussed which demonstrated a new approach using endocrine therapy for prevention of breast cancer in women who were at higher risk.

The future seems brighter due to research and innovation in the management of breast cancer. Clinical trials will continue to play a central role in future progress. A study by Esserman et al. is discussed that utilized a microarray gene expression analysis of RNA extracted from formalin-fixed paraffin-embedded primary tumor tissue from breast cancer patients. This study established a powerful MammaPrint risk stratification into either ultralow-, low- but not ultralow-, or high-risk categories that may have significant implications for how we personalize therapies for patients in the future.

Supportive care is essential for patients with breast cancer, and a representative trial that demonstrated the efficacy of denosumab in preventing skeletal-related events in patients with bone metastasis from breast cancer is included.

In summary, this chapter on Landmark Trials in Breast Cancer presents key findings from a selection of 24 trials. The reader is encouraged to refer to the full manuscripts of these trials for a greater understanding. These trials relate to the multidisciplinary management of breast cancer from the perspective of a radiation oncologist. There are many additional trials that could have been selected for inclusion. Therefore, no claim toward completeness can be made in the current format. Instead, this information is presented for educational purposes only and with the goal of encouraging further study about the landmark trials that have impacted oncology.

2.2 Breast Cancer

Fisher B, et al. NSABP-B04: Twenty-five year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med. 2002a;347(8):567–75.

The Halsted radical mastectomy was a disfiguring operation with significant side effects that, while used on hundreds of thousands of women throughout the world, had never formally been shown to improve overall survival over less aggressive surgery in a prospective randomized trial. As Bernard Fisher et al. stated in their landmark paper describing 25 years of follow-up of a randomized trial comparing radical mastectomy,

total mastectomy, and total mastectomy followed by irradiation, "the Halsted radical mastectomy, an en block removal of the breast, muscles of the chest wall, and contents of the axilla" had been the established and standard operation for breast cancer, even for small primary tumors, for much of the twentieth century. The results of the landmark NSABP-B04 trial rocked the establishment and changed the standard of care for patients who present with operable breast cancer, allowing for less aggressive surgery. The Halsted radical mastectomy, which had been performed unchallenged as the previous standard of care for almost a century, is rarely performed today.

The NSABP launched the B-04 clinical trial to evaluate whether local and regional treatments other than the Halsted radical mastectomy could achieve similar outcomes with less extensive surgery. The study accrued patients between 1971 and 1974. The study was set up as two parallel trials. A total of 1765 women with operable breast cancer were first divided into those who had clinically negative nodes and those who had clinically positive nodes. Women with clinical negative nodes were randomized (one-third in each arm) to Halsted radical mastectomy and axillary dissection, total mastectomy without axillary dissection but with regional irradiation, and total mastectomy plus axillary dissection only if their nodes became positive. Women who presented with clinically positive nodes were randomized (one-half to each arm) to radical mastectomy or total mastectomy and regional irradiation. None of the women received adjuvant systemic therapy.

The mean diameter of the largest primary tumor was 3.3 ± 2.0 cm and 3.7 ± 2.0 cm in women with negative and positive nodes, respectively. The radiation therapy was delivered tangentially to the chest wall to 5000 cGy in 25 fractions with node-positive patients receiving an additional boost dose of radiation. A dose of 4500 cGy in 25 fractions was administered to the supraclavicular and internal mammary nodes.

Key Point The study found no significant difference in disease-free survival, relapse-free survival, distant disease-free survival, or overall survival between the three groups with negative nodes (Tables 2.1 and 2.2).

Key Point The study found no significant difference in disease-free survival, relapse-free survival, distant disease-free survival, or overall survival between the two groups with positive nodes (Tables 2.1 and 2.3).

Table 2.1 Distribution of first events in NSABP B-04 trial for all patients

Event	All women ($N = 1665$)
Any event	1372 (82%)
Any recurrence other than contralateral breast	755 (45%)
Local recurrence	81 (5%)
Regional recurrence	108 (6%)
Contralateral breast cancer	105 (6%)
Second primary cancer other than breast	99 (6%)
Alive, event-free	293 (18%)

Table 2.2 Distribution of first events in NSABP B-04 trial for patients with clinically negative nodes

Event	Radical mastectomy ($N = 362$)	Total mastectomy ($N = 365$)	Total mastectomy plus radiation ($N = 352$)
Any event	281 (78%)	287 (79%)	292 (83%)
Any recurrence other than contralateral breast	135 (37%)	156 (43%)	131 (37%)
Local recurrence	19 (5%)	26 (7%)	5 (1%)
Regional	15 (4%)	23 (6%)	15 (4%)
Contralateral breast cancer	19 (5%)	26 (7%)	32 (9%)
Second primary cancer	23 (6%)	19 (5%)	28 (8%)
Alive, event-free	81 (22%)	78 (21%)	60 (17%)

Table 2.3 Distribution of first events in NSABP B-04 trial for patients with clinically positive nodes

Event	Radical mastectomy ($N = 292$)	Total mastectomy plus radiation ($N = 292$)
Any event	254 (87%)	258 (88%)
Any recurrence other than contralateral breast	165 (57%)	168 (57%)
Local recurrence	23 (8%)	8 (3%)
Regional	22 (8%)	33 (11%)
Contralateral breast cancer	13 (4%)	15 (5%)
Second primary cancer	12 (4%)	17 (6%)
Alive, event-free	38 (13%)	36 (12%)

In women with clinically negative nodes, the estimated disease-free survival at 25 years was 19, 13, and 19% for patients treated with radical mastectomy, total mastectomy with radiation, and total mastectomy alone, respectively. In women with clinically positive nodes, the estimated disease-free survival at 25 years was 11% and 10% for patients treated with radical mastectomy and total mastectomy plus radiation, respectively.

An interesting finding in NSABP B-04 was that 40% of women who presented with clinically negative nodes who went on to be treated with radical mastectomy with axillary dissection were found to have axillary lymph nodes pathologically positive for cancer. Fisher et al. estimated that because women were randomly assigned in this trial, that 40% of women who underwent total mastectomy alone had positive nodes that were not removed at the time of total mastectomy. However, only about half of these patients experienced positive axillary nodes as a first event, and there was no difference in distant recurrence or breast cancer-related mortality between these arms of the study.

Of the 365 patients with clinically negative axillary nodes who underwent total mastectomy without radiation therapy, 68 (18.6%) subsequently had pathologic confirmation of ipsilateral axillary nodal disease. The median time from initial surgery to identification of positive axillary nodes was 14.8 months (range of 3 to 134.5 months). Those patients who presented with clinically negative nodes who initially underwent total mastectomy without axillary dissection or radiation therapy that went on to develop pathologically positive nodes in the absence of other sites of disease underwent axillary dissection.

Local or regional recurrence varied among the group of patients presenting with negative nodes (the three-way statistical comparison $P = 0.002$) with the patients treated with total mastectomy and adjuvant radiation therapy experiencing the lowest cumulative incidence of local or regional recurrence. The overall cumulative incidence of dying either of recurrent cancer or after diagnosis of contralateral breast cancer was 40% in patients with negative nodes and 67% in women with positive nodes.

Fisher et al. concluded after 25 years of follow-up of their game-changing clinical trial, "The findings validate earlier results showing no advantage for radical mastectomy." The Halsted radical mastectomy was performed for nearly a century without randomized evidence supporting its use over less aggressive surgery in the management of breast cancer. The landmark NSABP B-04 trial changed the standard of care and had a beneficial impact for patients with breast cancer by lessening the burden of extensive surgery.

In awarding Dr. Bernard Fisher their prestigious award, the Lasker Foundation stated, "To Dr. Bernard Fisher, for his pioneering studies that have led to a dramatic improvement in survival and in the quality of life for women with breast cancer, this 1985 Albert Lasker Clinical Medical Research Award is given."

Fisher B, et al. NSABP B-06: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002b;347(16):1233–41.

There was an interest in further minimizing the extent of surgery in women with smaller primary breast tumors. Could breast conservation therapy reliably provide adequate control of breast cancer for properly selected patients? The NSABP B-06 study was initiated in 1976 to

evaluate whether lumpectomy with or without adjuvant radiation therapy was as effective as total mastectomy in the treatment of breast cancer in women with stage I or II disease with primary tumors less than or equal to 4 cm in diameter.

The study enrolled 2163 patients between 1976 and 1984. Patients with stage I or II disease with negative or positive nodes were randomized (one-third each arm) to either total mastectomy, lumpectomy, or lumpectomy plus adjuvant radiation therapy. Axillary dissection was done in each arm. The lumpectomy patients had their primary tumors removed with enough sufficient surrounding normal tissue to allow for a negative surgical margin and satisfactory cosmetic outcome. Level 1 and 2 axillary lymph nodes were dissected in the lumpectomy patients. For total mastectomy patients, the axillary nodes were removed en block with the primary tumor. The radiation therapy was delivered to a dose of 5000 cGy to the breast and not to the regional nodal region in patients randomized to the lumpectomy plus adjuvant irradiation arm of the trial. All node-positive patients underwent adjuvant chemotherapy with melphalan and fluorouracil. In patients with positive margins after lumpectomy, a total mastectomy was performed, and they were subsequently followed in their assigned randomization arm.

Key Point Twenty years after surgery, the cumulative rate of recurrence in the ipsilateral breast was 14.3% in patients assigned to lumpectomy plus irradiation and 39.2% in patients assigned to lumpectomy without irradiation ($P < 0.001$, Table 2.4).

There was no statistically significant difference in disease-free, distant disease-free, or overall survival between the three arms of the study. Adjuvant radiation therapy was associated with a marginal decrease in death from breast cancer (hazard ratio, 0.82; 95% confidence interval, 0.68 to 0.99; $P = 0.04$) which was partially offset by an increase in other causes of death (hazard ratio, 1.23; 95% confidence interval, 0.89 to 1.71; $P = 0.21$).

To address the concern that adjuvant radiation therapy may increase the risk of breast cancer in the contralateral breast, Fisher et al. reported that an increase in contralateral breast cancer was not observed in this study. As shown in accompanying Table 2.5, a significant portion of recurrences of breast cancer happened more than 5 years after initial surgery, underscoring the need for long-term follow-up for these patients.

The NSABP B-06 trial was a landmark trial that demonstrated that breast-conserving therapy consisting of lumpectomy followed by radiation

Table 2.4 The benefit of irradiation following breast conservation surgery was independent of nodal status. Shown is the cumulative incidence of recurrence for all breast conservation patients and node-negative and node-positive patients

B-06 20-year results	Recurrence rate lumpectomy alone	Recurrence rate lumpectomy plus irradiation	*P* value
All breast conservation patients	39.2%	14.3%	$P < 0.001$
Negative nodes	36.2%	17%	$P < 0.001$
Positive nodes	44.2%	8.8%	$P < 0.001$

Table 2.5 Time to first recurrence for total mastectomy, lumpectomy alone, and lumpectomy plus radiation for patients on NSABP B-06

Time to any first recurrence and years of follow-up	Total mastectomy	Lumpectomy alone	Lumpectomy plus radiation	Total
≤ 5 years	161 (74%)	187 (70%)	133 (62%)	481 (69%)
>5 and ≤ 10 years	38 (17%)	55 (20%)	49 (23%)	142 (20%)
>10 years	20 (9%)	27 (10%)	32 (15%)	79 (11%)

therapy could be performed in appropriately selected patients. After 20 years of follow-up, Fisher et al. reported "we found no significant difference in overall survival amongst women who underwent mastectomy and those who underwent lumpectomy." This study helped create randomized evidence that allows physicians to tailor the extent of surgery based on the size of the primary tumor and patient characteristics rather than the one-size-fits-all Halsted radical mastectomy that had been the previous standard of care for almost a century.

Fisher B, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol. 1998;16(2):441–52.

The NSABP B-06 study demonstrated that breast conservation therapy consisting of lumpectomy followed by radiation therapy was an appropriate treatment for properly selected patients with breast cancer. Would the same treatment paradigm apply to ductal carcinoma in situ? Was lumpectomy followed by radiation therapy an appropriate treatment for properly selected patients with ductal carcinoma in situ? The landmark NSABP B-17 study sought to answer this important question.

Between 1985 and 1990, the B-17 study recruited 818 women with ductal carcinoma in situ who underwent lumpectomy with histologically negative margins. Four hundred and five patients were randomized to receive lumpectomy alone and 413 to receive lumpectomy followed by radiation therapy. The radiation therapy was to 5000 cGy in standard fractions and started within 8 weeks of surgery.

Key Point With 8 years of follow-up, the incidence of noninvasive ipsilateral breast tumor was 13.4% versus 8.2% in favor of the adjuvant radiation therapy group ($P = 0.007$). The incidence of invasive ipsilateral breast tumor was 13.4% versus 3.9% in favor of the adjuvant radiation therapy group ($P < 0.0001$). There was a relative risk of failure of 1.74 (95% CI, 1.34 to 2.26) for patients treated with surgery alone versus surgery followed by radiation therapy (Table 2.6).

Table 2.6 Recurrence rates with 8 years of follow-up in NSABP B-17

8 years of follow-up	Lumpectomy alone	Lumpectomy plus radiation
Invasive ipsilateral breast tumor	13.4%	3.9%
Noninvasive ipsilateral breast tumor	13.4%	8.2%
Any ipsilateral breast tumor	26.8%	12.1%

The overall survival after 8 years follow-up was equivalent between the two arms of the study at 94% for patients treated with surgery alone and 95% for patients treated with surgery followed by radiation therapy ($P = 0.84$).

Fisher et al. stated that the use of radiation therapy following lumpectomy led to a reduced rate of both subsequent invasive and noninvasive ipsilateral breast tumors in women with localized DCIS detected on mammography. They examined the various pathologic characteristics of the DCIS specimens and found that "after the use of radiation therapy, not only did both good and poor risk patients benefit from radiation therapy, but their outcomes also became similar subsequent to the therapy." Fisher et al. concluded that treatment with lumpectomy and radiation therapy was the more appropriate treatment for localized DCIS compared with breast-conserving surgery alone.

Hughes K, et al. Cancer and Leukemia Group B (CALGB) 9343: Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31(19):2382–7.

Oncologists had observed that some older women tended to have less aggressive breast cancers. To test whether a favorable subgroup exists in which adjuvant irradiation may not provide a meaningful benefit, the CALGB conducted a randomized trial comparing postoperative tamoxifen alone versus tamoxifen plus radiation therapy in women with estrogen receptor-positive stage I breast cancer who had undergone breast conservation surgery with negative margins. The study enrolled 636 patients, 70 years of age and older, between 1994 and 1999.

Key Point After a median follow-up of 12.6 years, the 10-year incidence of local and regional recurrence-free survival was 98% in patients randomized to tamoxifen and radiation therapy and 90% in patients randomized to tamoxifen and no radiation therapy.

Key Point There is no significant difference between the two groups of patients in overall survival, breast cancer-specific survival, time to distant metastasis, or time to mastectomy (Table 2.7).

The patients treated with tamoxifen and radiation therapy had a significantly longer time to locoregional recurrence than the patients treated with tamoxifen without radiation therapy (observed HR, 0.18; 95% CI, 0.07 to 0.42; $P < 0.001$). The 10-year rates of being free from locoregional recurrence were 98% versus 90%, respectively, in the patients who did and did not receive radiation therapy.

Of the 636 patients enrolled on the study, only 21 deaths were a result of breast cancer. The 10-year breast cancer-specific survival rates were equivalent between the two arms at 97 and 98%, respectively.

Hughes et al. stated, "Importantly, the study also shows that the impact of breast cancer in this select group of older women is much smaller than that of comorbid conditions. Of the 636 women in this study, only 21 (3%) have died as a result of breast cancer, whereas 313 (49%) have died as a result of other causes (only 6% of deaths attributed to breast cancer)."

Table 2.7 Clinical outcome of patients enrolled on CALGB 9343

Treated patients	Tamoxifen plus radiation	Tamoxifen (no radiation)
Total patients	317	319
Recurrences	23	42
Ipsilateral breast recurrences alone	2	20
Axillary recurrences alone	0	5
Distant recurrences alone	17	10
All-cause deaths	166	168
Breast cancer-specific deaths	13	8

In summary, the CALGB 9343 trial provided data supporting another potential adjuvant management option for women aged 70 years and older with completed resected estrogen receptor-positive stage I breast cancer who agree to treatment with endocrine therapy. While radiation therapy provides a statistically significant decrease in locoregional recurrence, this did not translate into a significant difference in overall survival, distant disease-free survival, or time to mastectomy in this older group of patients with more favorable disease. Hughes et al. concluded that based on the importance placed on local recurrence, that tamoxifen was a reasonable option for appropriately selected women who were 70 years of age or older with completely resected, ER-positive, and early-stage breast cancer.

Krag D, et al. Sentinel lymph node resection compared with conventional axillary lymph node dissection in clinically node negative patients with breast cancer: overall survival findings from the NSABP B-32 randomized phase 3 trial. Lancet Oncol. 2010;11(10):927–33.

Could sentinel node biopsy offer a means to perform less aggressive surgery for the axillary lymph nodes, thereby reducing the morbidity associated with full axillary nodal dissection in some women with breast cancer? The sentinel node procedure had been introduced in the 1980s for its initial use in the management of malignant melanoma. The procedure was now poised to be adapted for the management of breast cancer.

Krag et al. stated that randomized trials such as NSABP B-06 had reduced the amount of surgery in appropriately selected patients. Krag et al. believed that the sentinel node procedure represented the next major opportunity to reduce the extent of surgery in properly chosen patients.

The NSABP B-32 trial randomized 5611 women with clinically negative lymph nodes to sentinel node resection plus axillary dissection (Group 1) or sentinel node resection alone with axillary dissection performed only if sentinel nodes were found to be pathologically positive

(Group 2). The patients in both groups who had negative sentinel nodes were then followed at 4- to 6-month intervals with primary outcomes of overall survival, disease-free survival, and regional control (Fig. 2.1). The study was designed to detect an overall survival difference of 2% at 5 years in sentinel node negative patients.

Sentinel node biopsy was performed using techtinium-99 m sulfur colloid and isosulfan blue dye. Pathologic assessment of nodes involved sectioning at 2 mm intervals and staining with hematoxylin and eosin. Routine immunohistochemistry was not permitted. Systemic therapy was administered to 85% and 84.1%, and radiation therapy was administered to 82.3% and 82.2% of group 1 and group 2 patients, respectively.

Key Point Regional control of disease, overall survival, and disease-free survival were statistically equivalent for both groups of patients (Fig. 2.2). When the sentinel node was pathologically negative, this important trial demonstrated that there was no advantage to proceeding with completion axillary dissection.

Key Point The 8-year estimate of overall survival was 91.8% and 90.3% for group 1 and group 2, respectively (HR 1.2, CI 0.96–1.50, $P = 0.12$). Regional recurrences occurred in 8 and 14 patients in group 1 and group 2, respectively ($P = 0.22$, see Table 2.8).

Key Point Patient-reported outcomes of pain, edema, and range of motion and sensory deficits were increased in patients who underwent full axillary lymph node dissection compared with sentinel node resection alone.

Therefore, this trial provided randomized evidence in support of lesser regional nodal surgery in sentinel node negative patients. The elimination

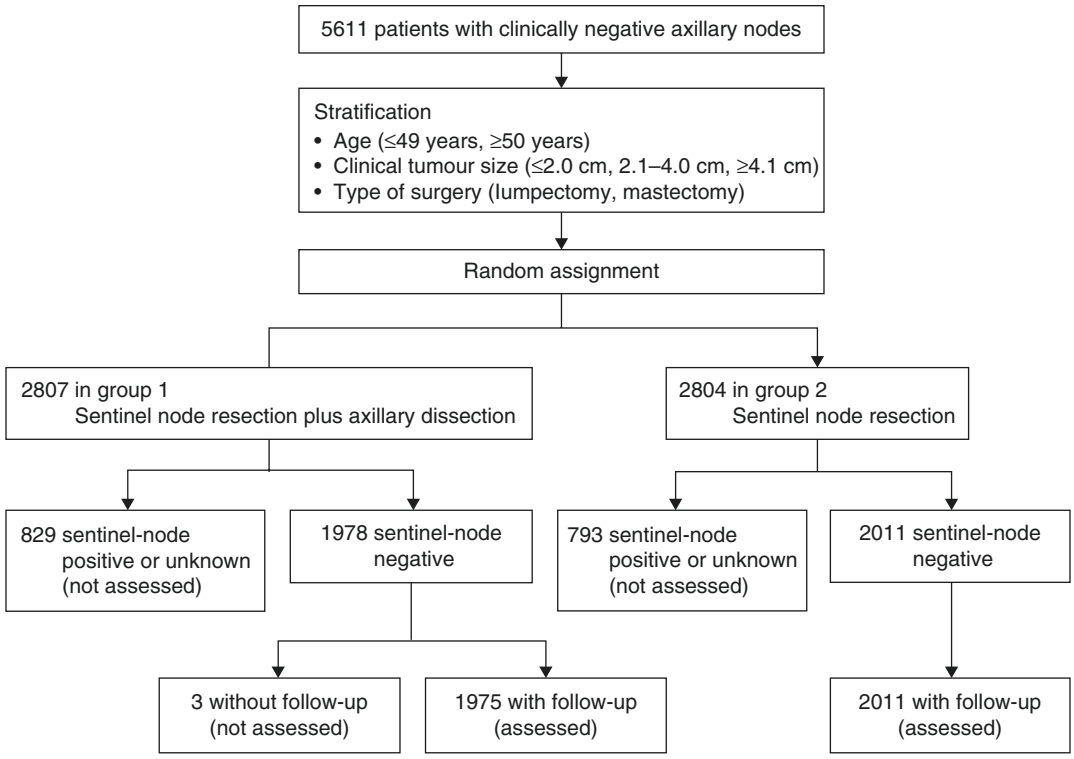

Fig. 2.1 Study schema for NSABP-B32. (Figure from Krag et al. Lancet Oncol. 11(10): 927–33, 2010 with permission)

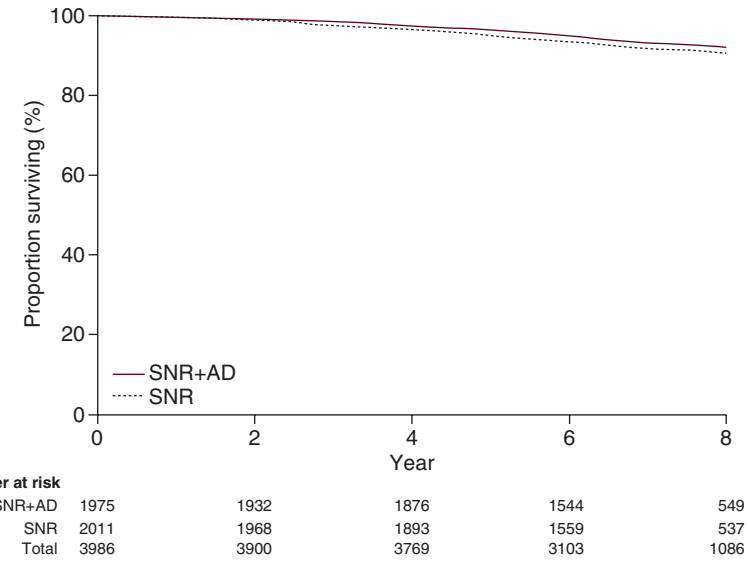

Fig. 2.2 Overall survival was equal in NSABP B-32 for patients with negative sentinel nodes who underwent either completion axillary lymph node dissection or sentinel node biopsy without axillary dissection. (Figure from Krag et al. Lancet Oncol. 11(10): 927–33, 2010 with permission)

Table 2.8 First reported site of treatment failure for patients with negative sentinel nodes

	Sentinel node resection + axillary dissection		Sentinel node resection	
Location of failure	No.	%	No.	%
Local recurrence	54	2.7	49	2.4
Regional node recurrence	8	0.4	14	0.7
Distant metastasis	55	2.8	64	3.2
Opposite breast	56	2.8	44	2.2
Second non-breast cancer	89	4.5	109	5.4
Dead, no evidence of disease	53	2.7	56	2.8
Total first events	*315*	*15.9*	*336*	*16.7*
Alive, event free	1660	84.1	1675	83.3
Patients followed	1975	100.0	2011	100.0

Table from Krag et al. Lancet Oncol. 11(10): 927–33, 2010 with permission

of full axillary dissection in these patients translated into improvements in quality of life.

Giuliano A, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis. the ACOSOG Z0011 (Alliance) randomized clinical trial. JAMA. 2017;318(10):918–26.

While axillary lymph node dissection can help maintain regional control in breast cancer, the surgery is associated with significant long-term morbidity including decreased range of motion, pain, numbness, and lymph edema risk. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial was designed to determine whether completion axillary lymph node dissection can be safely omitted in patients with one or two sentinel lymph node metastases detected by hematoxylin and eosin stain at the time of breast-conserving surgery, T1 or T2 disease, no palpable adenopathy at presentation, and who received adjuvant whole breast irradiation and adjuvant systemic therapy. In this trial, patients found to have one to two sentinel node metastases were randomized to no further axillary surgery or axillary lymph node dissection.

Patients were enrolled between 1999 and 2004. While the planned accrual goal was 1900 patients, the study closed having randomized 891 patients. The disease characteristics, demographics, radiation use and field design, and use of systemic therapy were well matched

between the two randomization arms. Radiation therapy was delivered in 89.6% of patients who underwent sentinel node dissection alone and 88.9% of patients in the axillary node dissection group. Even though the radiation therapy was supposed to be tangential whole breast radiation with a third supraclavicular regional nodal field prohibited, 18.9% of patients received protocol-prohibited nodal field radiation. Also, 11% of patients received no radiation therapy.

Key Point The 10-year overall survival rates were 86.3% and 83.6% in sentinel node and axillary dissection groups, respectively (HR 0.85; noninferiority $P = 0.02$). There was no difference in 10-year regional recurrence rates between the two groups (Table 2.9).

Micrometastasis were noted in 44.8% of sentinel node dissection patients and 37.5% of axillary dissection patients. Macrometastasis were noted 27.3% of the time in nonsentinel nodes in patients undergoing axillary dissection.

Giuliano et al. summarized that in this population of patients with early primary tumor stage and no palpable adenopathy, patients found to have one or two positive sentinel nodes experienced 10-year overall survival that was noninferior with sentinel node biopsy compared to patients treated with axillary dissection. Giuliano et al. stated that "these findings do not support routine use of axillary lymph node dissection in this patient population based on 10-year outcomes."

Donker M, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomized, multicenter, open label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15:1303–10.

The EORTC 10891–22023 AMAROS trial was initiated in 2001 when there was limited evidence supporting the sentinel node procedure and there were randomized trials that had compared axillary surgery to axillary radiation therapy in clinically node negative patients. The hypothesis of the AMAROS trial was that in stage T1 and T2 patients who were clinically node negative but found to have sentinel nodes pathologically positive for cancer, that regional nodal irradiation would be equivalent in terms of disease control to axillary dissection.

This randomized, multicenter phase 3 noninferiority trial enrolled 4823 patients between 2001 and 2010 (Fig. 2.3). The randomization was done before sentinel node biopsy. Of the 4823 patients enrolled, 1425 were found to have a positive sentinel node, and 744 patients were randomly assigned to axillary node dissection and 681 to axillary radiation therapy. Median follow-up for sentinel node-positive patients was 6.1 years.

Key Point In this multicenter prospective trial, both axillary node dissection and regional nodal irradiation provided excellent local-regional control of disease in stage T1 and T2 patients presenting with clinically negative nodes who were found to have a positive sentinel node biopsy. Axillary recurrences occurred in 4 patients in the dissection arm and 7 patients in the regional radiation arm, and the 5-year axillary recurrence rates were 0.43% and 1.19%, respectively. Donker et al. stated that far fewer axillary recurrences occurred than anticipated, so the trial was underpowered to detect a difference in its primary endpoint of regional nodal recurrence (Fig. 2.4).

Key Point Patients randomized to the axillary node dissection group experienced twice the rate of lymph edema as patients randomized to nodal irradiation. This is illustrated in accompanying Table 2.10 showing 5-year rates of lymph edema as detected by arm circumference measurement of 13% versus 6%, respectively.

Table 2.9 10-year rates of disease-free and overall survival in ACOSOG Z0011

	Sentinel node alone	Axillary dissection
10-year disease-free survival	80.2%	78.2%
10-year overall survival	86.3%	83.6%

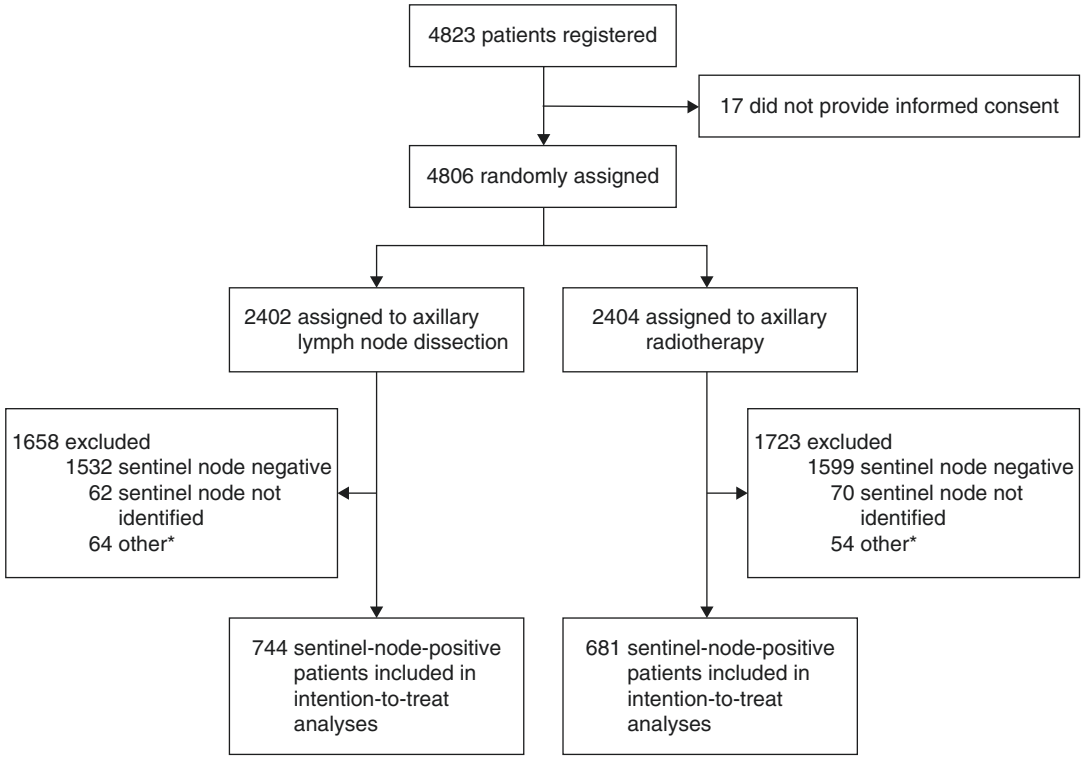

Fig. 2.3 Trial profile. *Includes patients who did not undergo sentinel node biopsy or whose sentinel node results were unknown (12 in the axillary lymph node dissection group and 12 in the axillary radiotherapy group), had only a positive nonsentinel node (16 and 6), had a positive sentinel node that was not located in the axilla (9 and 13), or only isolated tumor cells in the sentinel node after the protocol amendment (27 and 23). (Figure and legend from Donker et al. Lancet Oncol 2014; 15: 1303–10 with permission)

Donker et al. concluded that axillary radiation therapy is a valid treatment option instead of completion axillary dissection in the properly selected patient who presents with a clinically negative axilla and is found to have sentinel lymph node metastasis at the time of surgery.

Whelan T, et al. Regional nodal irradiation in early stage breast cancer. N Engl J Med. 2015;373:307–16.

The MA-20 trial randomized patients after breast-conserving surgery and sentinel node biopsy or axillary dissection to either whole breast radiation therapy or whole breast radiation therapy plus regional nodal irradiation including ipsilateral internal mammary nodes in the upper three intercostal spaces and supraclavicular and axillary nodes. To be eligible for this trial, women had invasive breast cancer and positive axillary nodes or negative axillary nodes with high-risk features such as primary tumor measuring at least 5 cm or primary tumor measuring 2 cm or more with fewer than 10 axillary nodes removed and at least 1 additional risk factor defined as grade 3 histology, ER-negative cancer, or lymphovascular space invasion.

The primary endpoint was overall survival, and there was no significant difference between the two groups in 10-year overall survival (82.8 versus 81.8%). In a pre-specified subgroup analysis, ER-negative patients did experience higher 10-year overall survival with the addition of regional nodal irradiation (81.3 versus 73.9%), and this difference approached statistical significance (hazard ratio, 0.69; 95% CI, 0.47 to 1.00; $P = 0.05$).

Key Point Disease-free survival was improved with regional nodal irradiation versus the control