Research and Audit in Advancing the Quality of Breast Cancer Care

Petra G. Boelens, Elma Meershoek-Klein Kranenbarg, Esther Bastiaannet, Cornelis van de Velde, and Riccardo A. Audisio

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63.1 Introduction

Breast cancer has been leading the way in adopting an evidence-based approach to improving outcomes. Breast cancer survival rates have increased substantially in the last 40 years, and the quality of life of survivors has been increased by better quality treatment following advances in breast surgery (breast conservation, oncoplastics, sentinel node biopsy and reconstruction), screening, radiotherapy and systemic therapies. All of these advances have been supported by research evidence highlighting its primacy in cancer care optimisation. This chapter will review research and audit methods and give examples of key studies that exemplify them.

63.2 Trial Design

There are many different types of research that may inform best practice in the field of breast cancer. It is of vital importance that the modern breast surgeon is aware of research methods, has the ability to perform critical evaluation of research data and keeps abreast of the latest trials and research to ensure they stay up to date. This chapter will focus on these issues giving examples of breast cancer research and audit to demonstrate each research type.

63.3 Study Types

There are many different types of research, and all may play an important role in improving the outcomes for women with breast cancer. The different types, their definitions and a classical example are shown below (Table 63.1) [1–18].

Another common way to classify trials is according to their phase as they progress from testing the basic physiological impact of the new intervention in vitro, in animal models (preclinical) and humans, to dose finding and ultimately confirmatory studies of safety and efficacy, at which point regulatory approval is usually granted. Refinements of use are then made in late phase studies (Table 63.2). All have a role in the evaluation of new treatments.

Table 63.1 Trial classification according to purpose

Trial purpose	Aim	Design	Breast cancer-specific examples
Breast cancer prevention	To identify ways to reducing the incidence of breast cancer	Cohort studies of lifestyle impacts, use of drugs in randomised trials	IBIS I and II NSABP P1 [1–4]
Breast screening	To identify effective ways to increase early diagnosis	Randomised trials, cohort study with bias correction	Swedish Two-County and other screening trials MARIBS trial of breast MRI screening FH01 trial of screening in high-risk women [5–7]
Diagnostic	To evaluate the efficacy of diagnostic tests, predictive and prognostic biomarker studies	Observational cohort or randomised trials to evaluate accuracy, sensitivity and specificity of new diagnostic tests	TAILORx and MINDACT are good examples of biomarker evaluation trials. Radiology trials to evaluate new means of staging the axilla such as that by Memarsadeghi 2006 [8, 9]
Treatment	To assess the efficacy of new drugs, surgical techniques and radiotherapy regimes	In surgery: often observational studies of case series and cohorts, some randomised studies [10, 11]. RCTs widely used in systemic therapy trials often with large meta-analyses to confirm findings	The AMAROS trial comparing axillary clearance and radiotherapy The ALMANAC trial comparing axillary clearance and SLNB The Early Breast Cancer Trialists' series of meta-analyses [12–15]
Quality of life and supportive care	To look at ways of improving the quality of life of cancer patients during and after treatment	Quantitative questionnaire design, validated quality of life tools, PROMs and qualitative research	Often integrated into many of the above trial designs. Good examples are the PRIME trial and the ALMANAC trial [16–18]

Table 63.2 Table describing the common phases of clinical trials

Phase	Aim
Preclinical studies	In vitro and animal studies
Phase 0	First in human studies to define pharmacodynamics and pharmacokinetics
Phase 1	Safety screening
Phase 2	Efficacy and dose finding
Phase 3	Comparative efficacy
Phase 4	Use optimisation in clinical practice

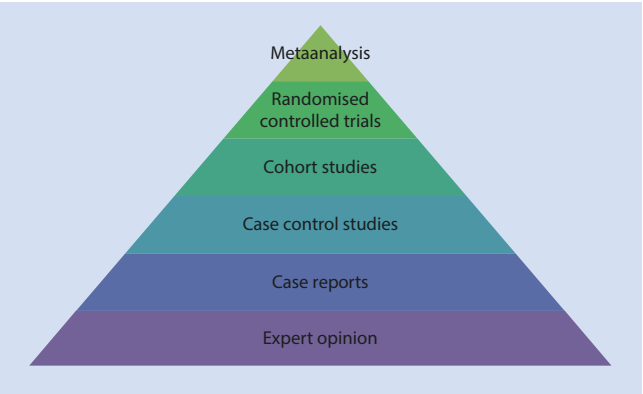

Fig. 63.1 Hierarchy of research evidence

63.4 Specific Research Methodologies and Research Quality Standards

63.4.1 Randomised Trials and Meta-Analyses

Randomised controlled trials (RCTs) and meta-analyses of data from such trials are considered the highest levels of evidence supporting clinical practice in oncology (Fig. 63.1).

The quality of the design and the quality control of these trials are of the utmost importance to warrant the safety, efficacy and reproducibility of the data and conclusions drawn from them. Surgical trials however have a number of challenges when compared to non-surgical trials. Choosing a homogenous patient population and an equivalent control group is challenging. Surgery, unlike a pill, is not a standardised, reproducible entity, but rather a unique product whose details are defined by variables, which include the skill of the surgeon. The skill level will not only vary among surgeons, but will increase for the same surgeon whilst he/she gains experience (surgical procedures have a learning curve) [19]. Furthermore, surgeons with a specific interest in a procedure will perform better [20]. These surgeons are also well disposed to develop new techniques in their own centre and subsequently analyse their series. This is one of the reasons why so many informative non-randomised hospital or personal series are published. RCTs in surgical oncology are therefore less common than cohort studies. Surgical versus non-surgical comparative trials also suffer from problems of lack of equipoise both on the part of the surgeon and the patient as the differences between treatments are often extreme. It is also difficult to blind the patient and surgeon to the intervention which may introduce bias.

There are some examples of well-designed trials comparing two surgical modalities or surgical versus non-surgical interventions. Trials such as those conducted by pioneering surgeons Umberto Veronesi in Europe and Bernard Fisher in the USA, comparing mastectomy versus breast-conserving therapy several decades ago, are excellent examples which lead to a massive change in practice in the field of breast cancer care [10, 11]. Trials that have successfully compared surgical and non-surgical options have also been conducted in breast care. An innovative, highly impactful and controversial trial compared standard axillary completion clearance with no further surgery in the ACOZOG 0011 trial [21]. This trial, whilst methodologically imperfect, has again changed global practices concerning axillary clearance in patients with low-risk clinically positive lymph nodes. Similarly the AMAROS trial, in which patients with T1–2 primary breast cancer and no palpable lymphadenopathy were randomised to receive either axillary lymph node dissection or axillary radiotherapy in cases with a positive sentinel node, concluded that radiotherapy gave excellent oncological results with less axillary morbidity [12]. As with trials in other surgical disciplines, breast surgery trials have also sometimes included a learning curve phase to ensure technical competency in the new technique. A good example of this was the ALMANAC trial of SLNB in breast cancer [1, 2, 18, 22]. There have been many advances in trial methodology in the past decade to ensure that data generated is valid and may be compared between studies. These have been formalised into trial guidelines such as the CONSORT statement for RCTs [23] and the PRISMA standards [24] for systematic reviews and meta-analyses. There are numerous other quality standards in action. It is essential that breast surgeons have a good understanding of how to assess the quality of research evidence so they can decide what is worthy of clinical adoption. There are a number of excellent overviews of how to critically assess the quality of research, a skill that should be an integral part of an oncologists' training [25–28].

In addition to randomised trials and meta-analyses, there are valid reasons why some research questions cannot be answered using this methodology. In the field of breast cancer, there are many such examples of where a cohort methodology is advantageous or the only feasible option.

63.4.2 Observational Studies (Cohort, Case Control)

Data from observational studies are increasingly used to fill knowledge gaps [29]. However, several challenges exist in the use of observational data: bias due to confounding by

indication is one of the major obstacles. This could potentially be tackled by using comparative effectiveness research if careful design and analysis is applied. For those research questions where randomised controlled trials are unethical, impractical or simply too lengthy for timely decisions, observational research may be used. The main problem with observational studies is treatment allocation bias which is difficult to fully adjust for in analysis. Patients who received a certain treatment typically differ from patients in whom that treatment is omitted. Excellent examples are patients treated non-surgically with primary endocrine therapy for operable cancer due to age, frailty or comorbidity will have higher morbidity and mortality rates than the fitter cohort who undergo the surgical option. Although it may be possible to adjust for factors that were measured, there will always remain certain factors that were unmeasured, so-called residual confounders [30]. The best example is frailty which is rarely formally assessed in studies but has a profound impact on treatment allocation and outcomes. Direct comparison of treatments can result in overestimation of treatment efficacy, and it is very likely that this problem occurs in most studies that have used this methodology. Although randomisation does not guarantee that treatment groups are equal across all possible confounding factors, it does guarantee that residual differences between groups are due to chance [30].

One of the more appropriate alternative methods that can be used to study treatment effectiveness in observational data is the use of instrumental variables. The instrumental variable is a factor that is associated with the allocation of a certain treatment, but is not directly associated with the outcome. For example, if two countries with comparable patients have a very different treatment strategy, the country may be used as the instrumental variable. Instead of comparing the outcome of patients with and without a certain treatment, differences in outcome between the two countries are compared, which eliminates bias due to confounding by indication [30]. There are three conditions that must be fulfilled for the use of an instrumental variable:

1. The instrumental variable must be related to the probability of receiving the treatment under investigation.
2. It should not be related to the prognosis of the patient.
3. It should not affect the outcome in any other way than through the treatment given [31].

The use of an instrumental variable is particularly useful in populations where randomisation is not feasible or not ethical [31], but it can be challenging to identify a proper instrumental variable that fulfils all three criteria. Still, when a good instrumental variable is available, it is considered to be the best method that can be used to study treatment effects in observational research [30].

Excellent examples of where observation studies have value are in areas where there are high levels of patient variability such that stratification with a randomised trial would be unfeasible. Research into the elderly is an excellent example of where observational data may be of value. Randomised trial inclusion of patients over the age of 70 is very limited with only 1–5% of the included patients older than 70 years, and there are a number of valid reasons for this. Not all older patients are suitable for standard treatments administrated to younger patients, and heterogeneity of the older population may complicate inclusion criteria [32]. Furthermore, early mortality – directly resulting from comorbid conditions – could reduce the apparent effectiveness, and shorter follow-up time will decrease statistical power to detect differences between treatment and control arms. Besides these methodological barriers, the participation and preferences of older patients and the willingness of otherwise of their clinicians may be considered another barrier. For all of these reasons, observational studies with appropriate adjustment for patient characteristics may be the only avenue to determine best practice in this age group.

63.4.3 Case Reports

For exceptionally rare conditions, running trials or even large observational studies may be impossible, and case reports may be the appropriate level of evidence to support best practice. In the field of breast cancer surgery, publication of case reports may ultimately lead to better understanding of rare associations, for example, the link between angiosarcoma and radiotherapy or the newly described but exceptionally rare breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) (▶ Chap. 29, breast implants).

63.5 Clinical Trials and Bias

A full understanding of bias and how it influences study results is essential for the practice of evidence-based medicine. Bias is defined as any factor of influence which prevents objective consideration of a question. Bias can occur at any phase of a study, including study design or data collection, as well as in the process of data analysis and publication. Breast surgeons must be trained to critically interpret study results and must also evaluate chosen endpoints, study design (patient population/controls) and identify study biases.

In clinical trials some forms of bias are always present; the issue is to what degree bias influences a favourable outcome for the test group (◘ Table 63.3) [33–35].

63.6 Clinical Trials and Funding

Cancer research in general is funded by different sources such as drug companies, charities, national governments and the European Union. Running randomised (double-blind), prospective clinical trials is time-consuming and costly. Costs involved in executing high-quality trials need to cover treatments, research staff to run the trial and collect the data,

Table 63.3 Different types of bias which may affect clinical research

Trial period	Bias	Definition	How to avoid
Planning the trial	Flawed study design	Many errors can occur in study design. Sample size should meet the power. Study groups should be equal, control treatment as equal as possible, endpoints adequate to answer to the hypothesis, time point adequate to test the hypothesis, etc.	Meticulous study design, power analysis, publish clinical trial study design, register trials, medical ethical committee approval before starting the trial
	Selection bias [33]	Comparing two different groups	Prospective design with unknown outcome reduces the likelihood of selection bias. Clear defined study population with inclusion and exclusion criteria for patients most at risk
	Randomisation or allocation bias	Use blinded treatment allocation	Researchers should not have a hand in allocation of treatments preferably by using computerised external randomisation
Bias during the trial execution	Interviewer bias	Questions to be asked should be standardised to avoid any suggestion of interviewers	Use blinding for group/outcome. Use validated questionnaires to avoid 'researcher's influence'
	Recall bias	Influence of the question in the recall of events happened in the past	Only use validated tools (questionnaires); use objective interviewers blinded to group and outcome
	Chronology bias	Historical data as control	Prospective design consecutive patients
	Performance bias	Variation in performance can influence outcome results	Standardise surgical techniques to minimise variation between surgeons
	Bias from misclassification	Misclassification of results or outcome due to variation in interpretation to classify results	Blinding for outcome, standardisation of data collection and outcome
	Transfer bias	Missing information due to subjects lost to follow-up	Reduce lost to follow-up as much as possible
After the trial	Publication bias [34]	The tendency of investigators to submit or the reviewers and editors to accept manuscripts based on the direction or strength of the study results	Reviewers and editors' responsibility to accept all decent quality research regardless of positive or negative findings
	Citation bias	Tendency of negative results not to be published and positive results to be published	Also publish negative results of studies Preregister trials
	Confounders	Any factor that correlates with dependent and independent variables	Control for confounders in the study design. Use stratification. Use double blinding and randomisation
	Internal vs external validity [35]	Internal validity denotes to the reliability or correctness of the study results External validity of study design refers to the degree to which findings are able to be generalised to other groups or populations	A study's internal validity reflects the investigator's and reviewer's confidence that study design, execution and data collection and analysis have reduced bias and that the findings are representative of the true association between exposure and outcome

costs of specific tests and laboratory analysis, costs of computer technology to analyse the results and administrative costs. The recently presented investigator-initiated MINDACT trial had a budget of €47 million [36]. Costly, large adjuvant trials with long-term follow-up and 'strong' endpoints are increasingly being replaced by cheaper, quicker, neoadjuvant trials with surrogate endpoints. The FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs for the treatment of serious conditions and to fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is defined as a marker, such as a laboratory measurement, radiographic image, physical sign or other measures, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.

The use of surrogate endpoints can considerably shorten the time required to receive (preliminary) FDA approval. Drug companies are still required to conduct studies to confirm the anticipated clinical benefit. These studies are known as phase 4 confirmatory trials. If the confirmatory trial shows that the drug actually provides a clinical benefit, then the FDA grants traditional approval for the drug. If the confirmatory trial does not show that the drug provides clinical benefit, FDA has regulatory procedures in place that could lead to removing the drug from the market [37]. Studies on surgical procedures are however generally not financed in a similar fashion. The lack of funds can also have a negative impact on the quality of the data. In financially supported drug trials, other issues are encountered. The main question to be answered is whether there is a reason for concern that pharmaceutical companies sponsor clinical trials which may introduce bias. Trial design might be optimised to gain regulatory approval, and staff may be selected who have a vested interest in seeing a positive result. In addition there is increasing concern about publication and citation bias with only trials showing positive results being published, whereas negative trial results are not published [34]. After a drug developing period, in which the companies invest in the new drug, the stakes are high to market newly designed drugs. Sponsorship of clinical trials by corporate industries can be as high as 75%. Pharmaceutical companies fund a large amount of cancer research and run their own trials looking at drugs they have developed [38].

Unfortunately, examples show that sponsors in the past have delayed publications or even stopped publications of unfavourable or negative outcomes. Moreover, the integrity of multiple scientists has been questioned for their unfair presentation of trial outcomes, even leading to withdrawal of publications in high-end journals and termination of academic careers [39]. The money involved in certain industry-financed projects can be huge. Conflict of interest statements must declare these links to enable the scientific community to be aware of potential bias.

Bias and errors in design and methodology should be screened for in industry-sponsored research for an objective representation of the study by journal reviewers, editors and readers. Many issues may obscure the study outcomes such as selection bias, inappropriate power calculation, sample size congruence, reasonable follow-up times, use of (invalidated) surrogate endpoints or the choice of the control agent or group. Selection can be detected by studying exclusion and inclusion criteria to see whether the included patients form a more favourable patient population, thereby contrasting with the 'real-world' patient population, excluding older patients and patients with comorbid diseases, or higher stages. In breast cancer investigation, follow-up time is of utmost importance to reveal true effects, and short follow-up times might be inappropriate. This is especially true in low-grade ER-positive breast cancer where outcomes such as local recurrence or death from breast cancer may not occur for well over a decade.

63.7 Quality Assurance in Breast Cancer Care: The Role of National and International Registries, Audits and Quality Standards

Breast cancer is the leading cause of cancer-related death among women [40]. Ensuring it is optimally treated is therefore of huge significance to female cancer mortality rates. There is wide variation in outcomes across European member states [41] due to differing rates of early diagnosis and different treatment protocols, and it is important that breast units have a systematic approach to critically reviewing the quality of their service against local, national and international standards. Service audits against these standards are an essential part of understanding where improvements can be made.

63.7.1 Guidance

There are a number of excellent quality standards and protocols that may be audited against, and all breast surgeons should be familiar with these. They include the St. Gallen Consensus Guidelines, the European Society of Breast Cancer Specialists (EUSOMA) and ESMO guidelines, National Guidelines such as the Dutch Breast Cancer Guidelines and the UK NICE guidelines. All of these are regularly updates by expert panels who synthesise the latest evidence in the field. It is also important that not only process and practice is audited but also outcomes which should be compared to national and international norms. Cancer incidence and mortality outcomes are collected by a range of national and international bodies. Internationally, the WHO collates these and publishes these as the GLOBOCAN data. Nationally, many European countries have mandatory reporting of cancer incidence and mortality rates via a series of cancer registries, many of which collect very detailed data about treatment, stage and outcomes. These may be used to undertake comparative audits between European countries. One of the international quality assurance initiatives, developed under the wings of the European Society of Surgical Oncology (ESSO) and the European Cancer Organisation (ECCO), is EURECCA, which is the acronym of European Registration of Cancer Care. EURECCA has a unique collaborative network of epidemiologists, patients and healthcare professionals.

63.8 Cancer Registries and Auditing

Registry of patient characteristics and therapeutic effects has been recognised as an extremely valuable source of information. Cancer registries have been collecting data for many decades, and their disease surveillance has shown distinct regional variations in breast cancer management and outcomes [42, 43].

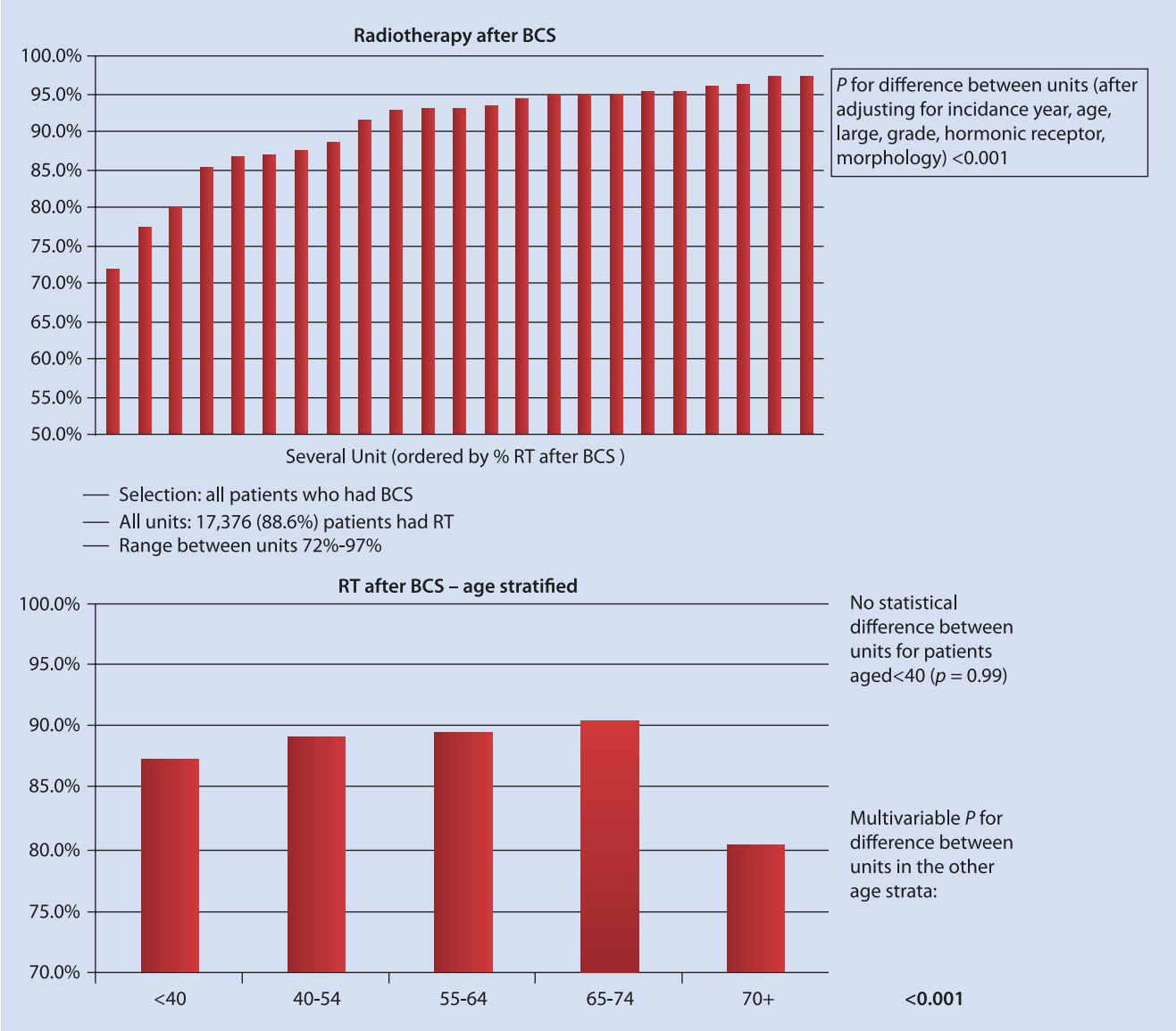

Fig. 63.2 Displays all patients receiving radiotherapy after breast-conserving surgery stratified to age groups, showing that the oldest patients received less radiotherapy after breast-conserving surgery

Auditing is combining data collection with feedback on performance to learn from best practice. In the last couple of decades, auditing cancer performance has been shown to be a powerful tool to improve regional and national healthcare infrastructures, for example, in rectal cancer [44, 45]. EURECCA was founded in 2007 by Prof Cornelis van de Velde, Professor of Surgical Oncology at Leiden University, the Netherlands, and EURECCA started with a colorectal working group. The main goals of EURECCA are to improve cancer outcomes by harmonising cancer data collection, providing feedback and developing guidelines and educational tools and sharing data across countries in prospective observational databases [46].

EURECCA Breast in collaboration with the European Society of Breast Cancer Specialists (EUSOMA) aims to improve and standardise the level of breast cancer patient care throughout Europe. The aim of this collaborative study was to assess age-specific compliance to the EUSOMA quality indicators (QIs) regarding treatment for patients across Europe [47]. Twenty-seven consented EUSOMA certified breast units from Austria, Belgium, Germany, Italy and Switzerland participated, and a dataset of 41,871 patients with a mean age of 59.6 years was available for analysis. The primary outcome measure was compliance with EUSOMA quality indicators (QIs) by age, selecting 13 QIs and using multivariable logistic regression analysis. This exceptional dataset demonstrated a low compliance to quality indicators among the youngest (<40 years) and the oldest (⩾75 years) patients (see example of one of the QIs in Fig. 63.1). Younger women were treated more than the guidelines recommended, whilst older patients less than recommended (see Fig. 63.2 [47]). Figure 63.1 shows the selection of patients who underwent breast-conserving surgery per breast unit. Of all patients in the dataset 88.6% underwent

BCS, ranging from 72% to 97% between breast units. Figure 63.2 shows examples of radiotherapy offered to patients undergoing breast-conserving therapy in the different breast units.

63.9 The Older Breast Cancer Patients in Observational Studies

EURECCA has a specific focus on older patients, which is a challenging heterogeneous subgroup of patients due to their wide variance in age, frailty and comorbidities. Forty per cent of breast cancer occurs in women 65 years and older. Most studies on therapeutic agents are selective in the inclusion of subjects and more often exclude women over a certain age and/or those with comorbidity. Irrespective of age, patients with breast cancer participating in trials had fewer comorbid diseases, smaller tumours and a higher socioeconomic status in comparison to unselected breast cancer patients from the Netherlands Cancer Registry [35]. Moreover, overall mortality of patients aged 65 years and older was lower for patients in trials as compared with patients of similar ages in the general population.

Taking into account that randomised controlled trials (RCTs) tend to exclude older women, prediction tools like Adjuvant! Online might lack validity to be used in medical decision-making in the older subset of patients with breast cancer. De Glas and colleagues entered data from the population-based cohort of all consecutive patients aged 65 years and older with breast cancer (n = 2012) into Adjuvant! Online with average for age comorbid status or individualised comorbid status. Primary outcome measures were a 10-year overall survival and 10-year cumulative recurrence, defined as locoregional recurrence, distant recurrence or contralateral breast cancer, in line with the definition of Adjuvant! Online. Adjuvant! Online did not predict these outcome measures accurately and is not representative of unselected older breast cancer population [3, 48].

In an international comparison of population-based data of older women with breast cancer, large differences in treatment approach were found with more guideline adherence on locoregional treatment in the Netherlands and more prescription of systemic therapy in Ireland. Authors concluded that their findings should be a strong recommendation to perform more international studies, with the ultimate goal of equalising survival rates for breast cancer patients across Europe [49]. A EURECCA International comparison is analysing treatment strategies and relative survival in more than 120.000 patients aged 70 years and older with non-metastatic breast cancer coming from the Netherlands, Belgium, Ireland, Portugal, Poland and the UK. Preliminary data presented at the European Cancer Conference in Amsterdam 2015 showed huge variations of treatment approaches in these age groups [50].

EURECCA Breast is planning to analyse data relating to changing axillary surgical practice subsequent to the recent groundbreaking Z11 [21] and AMAROS trials [12] and is recruiting patients in a prospective database for patients undergoing nipple-sparing mastectomies (INSPIRE), which will hopefully finally put to rest concerns about the oncological safety (or otherwise) of this technique.

63.10 Summary

The modern breast surgeon must keep up to date with the rapidly changing evidence base supporting optimal breast care to ensure patient outcomes maintain parity with the best in Europe. This requires the modern breast surgeon to develop critical appraisal skills so they may make their own judgements about the quality of new evidence and whether proposed changes in practice are justified. They must also continually evaluate their outcomes against national and European datasets to ensure they meet the highest standards, and if they find they do not, they must be responsive and change. Only in this way will they be able to ensure that they are delivering the very best care in this rapidly evolving field of cancer care.

References

1. Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 2014;383(9922):1041–8.
2. Forbes JF, Seccombe MA. Prevention and treatment trials need different recruitment strategies: experience from the IBIS 1 prevention trial in Australia and New Zealand. J Clin Oncol. 2004;22(14_suppl):1030.
3. Forbes JF, Sestak I, Howell A, Bonanni B, Bundred N, Levy C, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. Lancet. 2016;387(10021):866–73.
4. Goetz MP, Schaid DJ, Wickerham DL, Safgren S, Mushiroda T, Kubo M, et al. Evaluation of CYP2D6 and efficacy of tamoxifen and raloxifene in women treated for breast cancer chemoprevention: results from the NSABP P1 and P2 clinical trials. Clin Cancer Res. 2011;17(21):6944–51.
5. Warren RM, Thompson D, Pointon LJ, Hoff R, Gilbert FJ, Padhani AR, et al. Evaluation of a prospective scoring system designed for a multicenter breast MR imaging screening study. Radiology. 2006;239(3):677–85.
6. Gilbert FJ, Warren RM, Kwan-Lim G, Thompson DJ, Eeles RA, Evans DG, et al. Cancers in BRCA1 and BRCA2 carriers and in women at high risk for breast cancer: MR imaging and mammographic features. Radiology. 2009;252(2):358–68.
7. Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. Lancet Oncol. 2010;11(12):1127–34.
8. Rutgers E, Piccart-Gebhart MJ, Bogaerts J, Delaloge S, Veer LV, Rubio IT, et al. The EORTC 10041/BIG 03-04 MINDACT trial is feasible: results of the pilot phase. Eur J Cancer. 2011;47(18):2742–9.
9. Memarsadeghi M, Riedl CC, Kaneider A, Galid A, Rudas M, Matzek W, et al. Axillary lymph node metastases in patients with breast carcinomas: assessment with nonenhanced versus uspio-enhanced MR imaging. Radiology. 2006;241(2):367–77.

10. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227–32.
11. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. 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. 2002;347(16):1233–41.
12. Donker M, Van TG, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15(12):1303–10.
13. Goyal A, Newcombe RG, Mansel RE, Chetty U, Ell P, Fallowfield L, et al. Sentinel lymph node biopsy in patients with multifocal breast cancer. Eur J Surg Oncol. 2004;30(5):475–9.
14. Rocca A, Paradiso A, Sismondi P, Scarpi E, Mangia A, Medri L, et al. Benefit from CMF with or without anthracyclines in relation to biologic profiles in early breast cancer. J Clin Oncol. 2011 May 20;29(15_suppl):1031.
15. Barrett-Lee PJ, Bliss JM, Brunt AM, Dehshiri K, Harnett AN, Johnson L, et al. Polychemotherapy (CT) in pre- and post-menopausal women with early breast cancer prescribed 5 years tamoxifen (T) -results from the UK NCRI adjuvant breast cancer (ABC) international trial in 1991 patients. J Clin Oncol. 2004;22(14_suppl):656.
16. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015;16(3):266–73.
17. Williams LJ, Kunkler IH, King CC, Jack W, van der Pol M. A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial. Health Technol Assess. 2011;15(12):i–xi. 1-57
18. Goyal A, Newcombe RG, Chhabra A, Mansel RE. Morbidity in breast cancer patients with sentinel node metastases undergoing delayed axillary lymph node dissection (ALND) compared with immediate ALND. Ann Surg Oncol. 2008;15(1):262–7.
19. Clarke D, Newcombe RG, Mansel RE. The learning curve in sentinel node biopsy: the ALMANAC experience. Ann Surg Oncol. 2004;11(3 Suppl):211S–5S.
20. Mansel RE, McNeill F. Quality assurance in surgical trials of new techniques. J Clin Oncol. 2006 June 20;24(18_suppl):10584.
21. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305(6):569–75.
22. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. J Natl Cancer Inst. 2006;98(9):599–609.
23. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother. 2010;1(2):100–7.
24. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–12.
25. Greenhalgh T. How to read a paper. Statistics for the non-statistician. I: different types of data need different statistical tests. BMJ. 1997;315(7104):364–6.
26. Greenhalgh T. How to read a paper. Getting your bearings (deciding what the paper is about). BMJ. 1997;315(7102):243–6.
27. Greenhalgh T. How to read a paper. Statistics for the non-statistician. II: "significant" relations and their pitfalls. BMJ. 1997;315(7105):422–5.
28. Greenhalgh T. Assessing the methodological quality of published papers. BMJ. 1997;315(7103):305–8.
29. Hershman DL, Wright JD. Comparative effectiveness research in oncology methodology: observational data. J Clin Oncol. 2012;30(34):4215–22.
30. de Glas NA, Kiderlen M, de Craen AJ, Hamaker ME, Portielje JE, van de Velde CJ, et al. Assessing treatment effects in older breast cancer patients: systematic review of observational research methods. Cancer Treat Rev. 2015;41(3):254–61.
31. Chen Y, Briesacher BA. Use of instrumental variable in prescription drug research with observational data: a systematic review. J Clin Epidemiol. 2011;64(6):687–700.
32. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol. 2012;13(4):e148–60.
33. Lee J, Tanaka E, Eby PR, Zhou S, Wei W, Eppelheimer C, et al. Preoperative breast MRI: surgeons' patient selection patterns and potential bias in outcomes analyses. AJR Am J Roentgenol. 2016;27:1–10.
34. Soares HP, Kumar A, Daniels S, Sargent DJ, Buckner JC, Swann S, et al. Lack of publication bias in randomized clinical trials (RCTs) sponsored by the National Cancer Institute (NCI) and performed by cooperative oncology groups (COGs). J Clin Oncol. 2004;22(14_suppl):6004.
35. van de Water W, Kiderlen M, Bastiaannet E, Siesling S, Westendorp RG, van de Velde CJ, et al. External validity of a trial comprised of elderly patients with hormone receptor-positive breast cancer. J Natl Cancer Inst. 106(4):dju051.
36. http://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx?ItemID=867#.V2zt-f5f2Uk. 2017. Ref Type: Generic.
37. http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm313768.htm. 2017. Ref Type: Generic.
38. Braend AM, Straand J, Jakobsen RB, Klovning A. Publication and non-publication of drug trial results: a 10-year cohort of trials in Norwegian general practice. BMJ Open. 2016;6(4):e010535.
39. Antman K. Randomized trials of high-dose chemotherapy in breast cancer: fraud, the press and the data (or lessons learned in medical policy governing clinical research). Trans Am Clin Climatol Assoc. 2002;113:56–66.
40. Ly D, Forman D, Ferlay J, Brinton LA, Cook MB. An international comparison of male and female breast cancer incidence rates. Int J Cancer. 2013;132(8):1918–26.
41. Thomson CS, Forman D. Cancer survival in England and the influence of early diagnosis: what can we learn from recent EUROCARE results? Br J Cancer. 2009;101(Suppl 2):S102–9.
42. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO, Jemal A. International variation in female breast cancer incidence and mortality rates. Cancer Epidemiol Biomark Prev. 2015;24(10):1495–506.
43. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374–403.
44. Breugom AJ, Boelens PG, van den Broek CB, Cervantes A, Van CE, Schmoll HJ, et al. Quality assurance in the treatment of colorectal cancer: the EURECCA initiative. Ann Oncol. 2014;25(8):1485–92.
45. Van GW, Van den Broek CB, Mroczkowski P, Dziki A, Romano G, Pavalkis D, et al. The EURECCA project: data items scored by European colorectal cancer audit registries. Eur J Surg Oncol. 2012;38(6):467–71.
46. Van GW, Van de Velde CJ. Improving quality of cancer care through surgical audit. Eur J Surg Oncol. 2010;36(Suppl 1):S23–6.
47. Kiderlen M, Ponti A, Tomatis M, Boelens PG, Bastiaannet E, Wilson R, et al. Variations in compliance to quality indicators by age for 41,871 breast cancer patients across Europe: a European Society of Breast Cancer Specialists database analysis. Eur J Cancer. 2015;51(10):1221–30.

48. de Glas NA, van de Water W, Engelhardt EG, Bastiaannet E, de Craen AJ, Kroep JR, et al. Validity of adjuvant! Online program in older patients with breast cancer: a population-based study. Lancet Oncol. 2014;15(7):722–9.
49. Kiderlen M, Walsh PM, Bastiaannet E, Kelly MB, Audisio RA, Boelens PG, et al. Treatment strategies and survival of older breast cancer patients – an international comparison between the Netherlands and Ireland. PLoS One. 2015;10(2):e0118074.
50. Derks M, Kiderlen M, Hilling D, Bastiaannet E, Boelens PG, Siesling S, et al. Treatment patterns for older patients with non-metastatic breast cancer in four European countries - preliminary data from a EURECCA international comparison. Eur J Cancer. 2015;51:S297. Ref Type: Generic