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Cost-utility analysis of four common surgical treatment pathways for breast cancer

Casimir A.E. Kouwenberg [a, b, *], Marc A.M. Mureau [a], Leonieke W. Kranenburg [b], Hinne Rakhorst [c], Daniëlle de Leeuw [d], Taco M.A.L. Klem [e], Linetta B. Koppert [f], Isaac Corro Ramos [g], Jan J. Busschbach [b]

[a] Department of Plastic and Reconstructive Surgery, Erasmus MC Cancer Institute, University Medical Centre Rotterdam, Rotterdam, the Netherlands
[b] Department of Psychiatry, Section Medical Psychology and Psychotherapy, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, the Netherlands
[c] Department of Plastic, Reconstructive and Hand Surgery, Hospital Medisch Spectrum Twente/ Hospital Group Twente, Enschede, the Netherlands
[d] Department of Surgery, Hospital Group Twente, Almelo, the Netherlands
[e] Department of Surgery, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands
[f] Department of Surgical Oncology, Erasmus MC Cancer Institute, University Medical Centre Rotterdam, Rotterdam, the Netherlands
[g] Institute for Medical Technology Assessment (iMTA), Erasmus University Rotterdam, Rotterdam, the Netherlands

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ABSTRACT

Background: The aim was to evaluate the cost-utility of four common surgical treatment pathways for breast cancer: mastectomy, breast-conserving therapy (BCT), implant breast reconstruction (BR) and autologous-BR.

Methods: Patient-level healthcare consumption data and results of a large quality of life (QoL) study from five Dutch hospitals were combined. The cost-effectiveness was assessed in terms of incremental costs and quality adjusted life years (QALYs) over a 10-year follow-up period. Costs were assessed from a healthcare provider perspective.

Results: BCT resulted in comparable QoL with lower costs compared to implant-BR and autologous-BR and showed better QoL with higher costs than mastectomy (€17,246/QALY). QoL outcomes and costs of especially autologous-BR were affected by the relatively high occurrence of complications. If reconstruction following mastectomy was performed, implant-BR was more cost-effective than autologous-BR.

Conclusion: The occurrence of complications had a substantial effect on costs and QoL outcomes of different surgical pathways for breast cancer. When this was taken into account, BCT was most the cost-effective treatment. Even with higher costs and a higher risk of complications, implant-BR and autologous-BR remained cost-effective over mastectomy. This pleas for adapting surgical pathways to individual patient preferences in the trade-off between the risks of complications and expected outcomes.

Introduction

One in eight women will develop breast cancer in her lifetime [1–3]. Surgical treatment pathways for early-stage breast cancer patients consist of either breast-conserving surgery (BCS) or mastectomy [4,5]. The advantage of BCS over mastectomy is preservation of the breast contour, thereby optimizing cosmetic outcome of the affected breast [4]. However, BCS needs to be followed by adjuvant radiotherapy, known as breast-conserving therapy (BCT), to reach oncological outcomes similar to mastectomy [6–8]. Some patients therefore prefer mastectomy because of concerns about radiation effects or disease recurrence in case of BCT [9] or may require mastectomy based on contra-indications for BCS or radiotherapy [4,5].

Because loss of a breast may negatively affect psychological health, body image, and sexual function [10,11], (inter)national guidelines recommend that the possibility of postmastectomy breast reconstruction (BR) should be discussed with every patient

* Corresponding author. Department of Plastic and Reconstructive Surgery, Erasmus MC Cancer Institute, University Medical Centre Rotterdam, PO Box 2040, 3000 CA, Rotterdam, the Netherlands.,
E-mail addresses: c.kouwenberg@erasmusmc.nl, kouwenberg@gmail.com (C.A.E. Kouwenberg).

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with an indication for mastectomy [4,5,12]. Multiple BR options are available, either using autologous tissue with a pedicled or free flap (autologous-BR) or breast implants (implant-BR), varying in costs, timing, duration, complication rates, and cosmetic results [10,13,14]. Postmastectomy BR aims to improve the patient's well-being and quality of life (QoL) [10,11,13], but patients opting for BR also have a risk of complications [15–18], reconstruction failure [15,16], or disappointing (cosmetic) outcomes [10]. Consequently, shared decision-making between physician and patient on which surgical treatment is preferred comprises a complex trade-off between risks and outcomes.

Beside considering risks and benefits for the patient in choosing treatment modalities, different treatment pathways have different costs. In the current times of scarcity of healthcare budgets, it is relevant to know which intervention provides the most benefit (i.e., health) per dollar or euro. This is not only relevant when choosing between surgical options for breast cancer, but this is also relevant when the reimbursement of these surgical options is in competition with other allocations of the health care budget. In that respect, BR is in a vulnerable position, as it aims at improving quality of life rather than survival. Evidence that a given surgical treatment has a favorable cost-effectiveness will help to strengthen its position if scarcity in healthcare budgets emerge.

Evidence about the cost-effectiveness of aforementioned common surgical treatment pathways for breast cancer compared to other allocations of budget in healthcare is only meaningful if it is possible to directly compare the outcomes of these surgical treatment pathways with other medical interventions. The formal way to do so is to perform a 'cost-utility analysis', as indicated in literature and guidelines on health economics [19–23]. This is a special case of cost-effectiveness analysis where QoL outcomes are defined in generic terms, Quality Adjusted Life Years (QALYs), so that different interventions can be directly compared. State-of-the-art QALY analysis uses specific validated questionnaires such as the EQ-5D to estimate QALYs [20,23–25].

A recent meta-analysis compared 16 studies which have investigated the cost-effectiveness of DIEP-flap and implant-based BR techniques [26]. The authors concluded that DIEP-flap BR may be more cost-effective and yields superior patient-reported outcomes. However, the quality of the included studies was considered poor, showing high degrees of bias. Moreover, in a large cross-sectional study by Kouwenberg et al., after controlling for differences in pre-treatment patient characteristics, this superiority of autologous-BR over implant-BR was not reproducible using a generic QALY measure [11]. No statistically significant differences in EQ-5D outcomes/utilities could be found between patients following BCT, implant-BR and autologous-BR, but all three patient groups had significantly better outcomes/utilities than mastectomy patients [11].

The aim of the present study was to compare the cost-effectiveness of the four most common surgical breast cancer treatment pathways (mastectomy without BR, BCT, mastectomy followed by implant-BR, and mastectomy followed by autologous-BR) using state-of-the-art methods.

Methods

Summary

The purpose of this multicenter observational cohort study was to compare four common surgical treatment pathways (mastectomy, BCT, implant-BR and autologous free vascularized BR (autologous-BR)) for breast cancer patients using real patient-level healthcare consumption registration data for all patients who had undergone surgical breast cancer treatment in four general and one academic hospital in the Netherlands between January 1st, 2005 and January 1st, 2017. The four treatment pathways were compared on their relative costs of major care categories (surgical interventions, radiotherapy, outpatient visits, admission days and diagnostics related resources), costs of complications during the treatment pathway and QoL on an intention-to-treat basis. From these figures, the cost-effectiveness was assessed in terms of the incremental ratio of costs and QALYs (ICER) over a 10-year follow-up period. In addition to a full-incremental analysis in which all available options were compared to another, also pairwise comparisons were performed. A 10-year period was chosen, as costs for BR are incurred over a longer period of time. Costs were assessed from a healthcare provider perspective based on Dutch unit costs. Costs and QALYs were discounted with a rate of 4% and 1.5% per year, respectively [24]. QALY-weights (EQ-5D-5L utility-values) of the relevant health states were available from previous research of our group [11]. A complete follow-up period of 10 years was not available for all patients because of the continued inclusion in the cohort, which led to right censoring of the cost and health utility data. A large proportion of autologous-BR patients had received their oncological breast cancer treatment at a different hospital than one of the participating hospitals. Consequently, the data on the oncological surgery part of their treatment was not available for these patients. These two types of missing data were addressed using multiple imputation with chained equations, using predictive mean matching that accounts for uncertainty in the respective treatment arm, which is also appropriate for cost and utility data that is non-normally distributed [27]. Furthermore, three scenario sensitivity analyses were performed to explore the effects of different scenarios regarding 1) OR costs, 2) re-operation rates for implant-BR and 3) complication rates for autologous-BR.

The Medical Ethics Committee of the Erasmus MC reviewed and approved the study protocol (MEC-2015-273). The methods are elaborated in detail in the Appendix.

Results

In total, 3706 mastectomy, 3553 BCT, 621 implant-BR and 513 autologous-BR patients were included in the present analysis. The patient characteristics of the different intention-to-treat treatment pathways are listed in Table 1. Most notable is the relatively higher age in the mastectomy and BCT cohorts compared to the BR cohorts.

Cost-analysis and cost-effectiveness

Mean costs per cost category per treatment pathway, which are further addressed in the next paragraphs, are shown in Table 2 and Fig. 1. Fig. 2 shows the histograms of the total incurred costs per patient for each of the different treatment pathways and provides more insight in the variability and distribution of the costs among the different treatment pathways. The higher peaks and narrower distribution of the mastectomy and BCT groups show that there was less variability in the total costs of these treatments compared to implant-BR and autologous-BR. One autologous-BR patient had incurred very high costs (€401,953) in her treatment pathway, due to a severe, chronic auto-inflammatory syndrome. This outlier is not shown in Fig. 2.

Oncological surgery costs

Over the course of 10 years, BR led to substantially higher mean oncological surgery costs compared to mastectomy and BCT, which can primarily be attributed to operation related costs and outpatient clinic costs. BCT had lower admission and OR costs compared to mastectomy but was associated with higher diagnostics costs.

Table 1
Characteristics of 8393 breast cancer patients by surgical treatment pathway.

Mean (SD)	MAS	BCT	I-BR	A-BR
	N 3706 (44.16%)	3553 (42.33%)	621 (7.4%)	513 (6.11%)
Age at BC Dx	62.9 (13.9)	59.2 (11.4)	49.2 (10.6)	48.2 (10.6)
Follow up in months	83.0 (52.1)	91.8 (49.9)	96.4 (48.8)	86.9 (50.8)
Immediate BR	NA	NA	55.39%	0%
BCS Conversion <6 m	NA	1.18%	NA	NA
BR Conversion	NA	NA	8.86%	0.78%
Reoperations within 60 days				
0	77.39%	75.46%	57.97%	75.05%
1	20.18%	21.5%	31.88%	15.01%
2-3	2.37%	2.84%	9.34%	8.38%
>3	0.05%	0.2%	0.81%	1.56%
Reoperations within 45 days				
0	78.49%	77.09%	60.55%	75.63%
1	19.43%	20.63%	30.11%	14.81%
2-3	2.02%	2.11%	8.7%	8.19%
>3	0.05%	0.17%	0.64%	1.36%
Mean number admission days	4.8	3.3	8.8	9.7
Hospital type				
General	83.00%	85.61%	83.57%	8.97%
Academic	17.00%	14.38%	16.43%	91.03%

MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction.

Table 2
Cost-effectiveness outcomes over a 10-year period by surgical treatment pathway.

		MAS	BCT	I-BR	A-BR
Mean costs					
Oncologic Surgery					
Total		€ 9066	€ 8543	€ 9977	€ 10 075
Discounted Total		€ 8749	€ 8164	€ 9610	€ 9638
Subtotals:					
Operation		€ 2479	€ 2285	€ 2804	€ 3677
Non-OR:		€ 6588	€ 6258	€ 7173	€ 6397
First 3 years	Outpatient	€ 1206	€ 1125	€ 1396	€ 1712
	Admission	€ 2117	€ 1301	€ 2059	€ 1452
	Diagnostics	€ 2049	€ 2329	€ 2296	€ 2027
Plastic Surgery					
Total		€ 486	€ 1093	€ 9578	€ 15 004
Discounted Total		€ 441	€ 991	€ 8843	€ 13 728
Subtotals:					
Operation		€ 104	€ 436	€ 5261	€ 7669
Non-OR:		€ 383	€ 657	€ 4317	€ 7335
First 8 years	Outpatient	€ 219	€ 314	€ 1724	€ 2174
	Admission	€ 101	€ 247	€ 2014	€ 4459
	Diagnostics	€ 28	€ 47	€ 193	€ 602
Radiotherapy		€ 1743	€ 7606	€ 823	€ 2480
Overall undiscounted total		€ 11 296	€ 17 242	€ 20 377	€ 27 559
Overall discounted total		€ 10 933	€ 16 761	€ 19 275	€ 25 846
Undiscounted QALY's accrued		8.05	8.41	8.40	8.41
Discounted QALY's accrued		7.53	7.87	7.85	7.85

MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction, QALY: quality adjusted life year. Applied discounting rates: minus 4% per year for costs, minus 1.5% per year for effects.

Plastic surgery costs

The mean total costs for plastic surgery care for autologous-BR were €5426 or 57% higher than for implant-BR over the course of 10 years. Compared to implant-BR, almost all of the additional costs of autologous-BR were associated with admission costs €2445 or 121% higher, and operation related costs €2408 or 46% higher.

Radiotherapy costs

As expected, BCT had the highest costs for radiotherapy (€7606), representing almost half of the total costs associated with the BCT treatment pathway. Conversely, implant-BR had the lowest radiotherapy costs which is probably due to the relative contraindication for implant-BR with radiotherapy.

Quality adjusted life years (QALYs)

No substantial differences existed between the aggregated QALYs of BCT, implant-BR and autologous-BR. However, these three surgical treatments did have a substantial QALY gain over mastectomy of 0.34, 0.32, and 0.31, respectively, over a 10-year period after discounting.

Incremental cost effectiveness ratio (ICER)

The incremental cost-effectiveness ratios over a 10-year period by surgical treatment pathway are shown in Table 3. Because of the slightly better QALY effects and the substantial lower costs, the full-incremental analysis showed BCT to 'dominate' both implant-BR and autologous-BR and was the most cost-effective treatment.

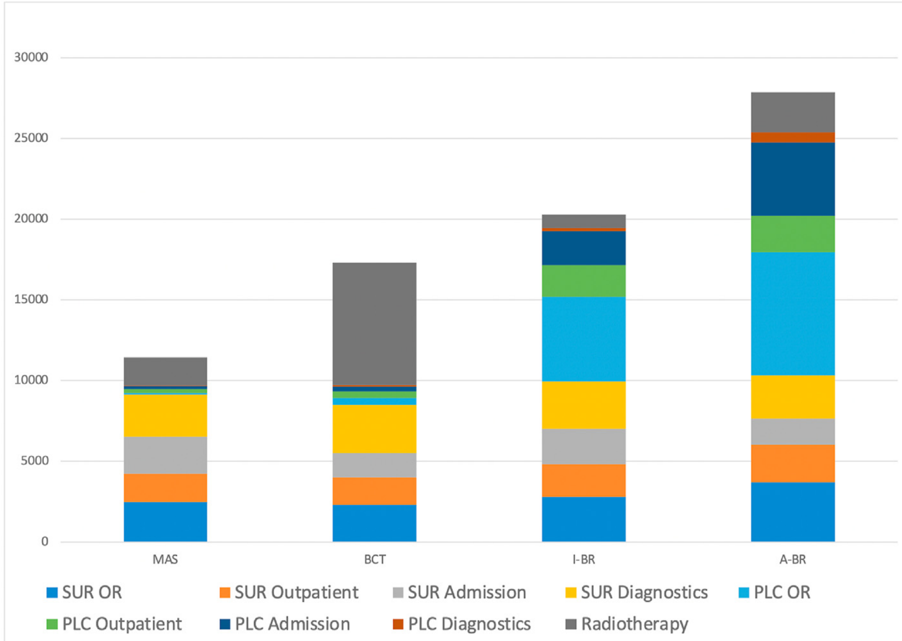

Fig. 1. Average costs (in euros) per cost-category for each of the four different treatment pathways over a 10-year period MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction. SUR: surgical oncology, PLC: plastic surgery, OR: operation related costs, Outpatient: outpatient related costs, Admission: admission related costs, Diagnostics: diagnostics related costs.

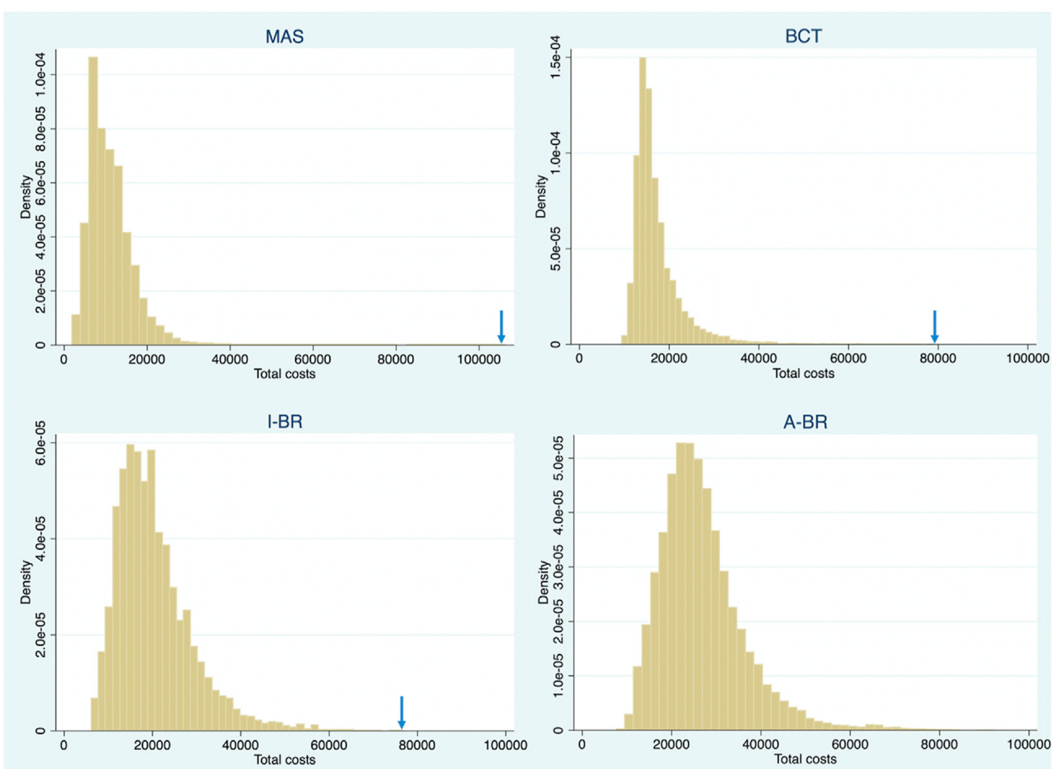

Fig. 2. Histograms of total costs (in euros) per individual patient for each treatment pathway. MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction. The arrows signify the patient with the highest costs in the treatment group. Please note that the one outlier in the autologous-BR group with costs of €401 953 is not depicted in the histogram. For this reason, no arrow indicating the patient with the highest costs is depicted for A-BR.

Table 3
Incremental cost-effectiveness ratio over a 10-year period by surgical treatment pathway.

			MAS	BCT	I-BR	A-BR
Pairwise: Incremental cost-effectiveness ratio, undicsounted (€/QALY)						
vs MAS			NA	16 521	28 406	51 715
vs BCS					Dom. by BCS	16 227 856
vs I-BR						537 933
Pairwise: Incremental cost-effectiveness ratio, discounted (€/QALY)						
vs MAS			NA	17 246	26 093	47 422
vs BCS					Dom. by BCS	Dom. by BCS
vs I-BR						Dom. by I-BR
Full-incremental CE analysis	QALYs	Costs	Incremental QALYs		Incremental Costs	ICER
MAS	7.53	€ 10 933				
I-BR	7.85	€ 19 275			Dominated by BCS	
A-BR	7.85	€ 25 846			Dominated by BCS*	
BCS	7.87	€ 16 761	0.34		€ 5828	€ 17 246

MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction. Applied discounting rates: minus 4% per year for costs, minus 1.5% per year for effects. Note that both pairwise and full incremental cost-effectiveness analysis are presented, only the full-incremental analysis takes all the available treatment into account in its assessment. If a treatment is cheaper and more effective it dominates the other treatment (Dom.). The differences between QALY gains can be small, cost effectiveness ratios can be extremely large, as differences in costs are divided by a very small QALY effect.

This means that BCT was more effective with less costs. Note when the differences between QALY gains become as small as in this investigation, cost-effectiveness ratios can be extremely large, as differences in costs were divided by a very small QALY effect.

Complication related costs

Table 4 shows an overview of the cost differences between surgical pathways with and without an additional surgical intervention within 60 days. The impact of complications on the costs was substantial, even up to 80% increase in plastic surgery related costs after autologous-BR.

Sensitivity analyses

Raising or lowering the OR costs by 20% did not lead to any substantial changes in the relative cost-effectiveness between treatments. In the second scenario sensitivity analysis, a worst-case scenario assumption was made that all implant-BR patients needed to undergo a re-operation in year 10 for implant replacement and for which all associated additional costs were taken into account. After simulating this worst-case scenario, autologous-BR would still be over €4500 (+21%) more expensive than implant-BR. The third scenario sensitivity analysis showed that reductions in complication rates may bring the ICER between implant-BR and autologous-BR down quickly from the very high value we found in our study, to more acceptable levels from an estimated €80,000/QALY after a 40% reduction in complication rates to even below €50,000/QALY following a 60% reduction.

Discussion

The present cost-effectiveness analysis of the four most common surgical treatment pathways for breast cancer suggests that BCT is the most cost-effective treatment option if the breast mound is either preserved or reconstructed. Both implant-BR and autologous-BR were considerably more expensive than BCT, with no additional QALY benefits, which made that they did not classify as cost-effective alternatives over BCT.

Longitudinal costs studies which compared autologous-BR and implant-BR have shown mixed results; some found higher costs associated with autologous-BR, while others reported similar or lower costs associated with autologous-BR [28–35]. Pinpointing where these differences arise from is complex due to the aggregated character of the results, differences in methods, reimbursement systems and practices, and last but not least, possible difference in success rates and quality of the local surgical interventions.

Table 4
Cost differences between surgical treatment pathways with and without complications.

	MAS		BCT		I-BR		A-BR	
Mean costs difference								
Oncologic Surgery	+€4046	+50%	+€3637	+48%	+€2821	+32%	+€1353	+14%
Operation	+€1694	+81%	+€1736	+93%	+€1280	+56%	+€677	+19%
Outpatient	+€136	+12%	+€198	+18%	+€153	+11%	+€113	+7%
Admission	+€1531	+86%	+€1372	+142%	+€946	+57%	+€215	+15%
Diagnostics	+€297	+15%	+€87	+4%	+€271	+12%	+€283	+14%
Plastic Surgery	+€434	+112%	+€1040	+124%	+€2996	+36%	+€10,009	+80%
Operation	+€163	+243%	+€547	+181%	+€1467	+32%	+€4682	+72%
Outpatient	+€67	+33%	+€163	+60%	+€280	+17%	+€980	+51%
Admission	+€178	+294%	+€293	+167%	+€1061	+68%	+€3479	+97%
Diagnostics	+€18	+74%	+€28	+69%	+€74	+46%	+€658	+150%
Radiotherapy	-€1	+0%	+€53	+1%	+€55	+7%	-€516	−20%
Total costs	+€4478	+44%	+€4729	+29%	+€5871	+33%	+€10,846	+44%

Absolute (in euros) and relative (in %) mean cost differences between treatment pathways with and without complications. MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction. A treatment pathway with postoperative complications was defined as patients who were re-operated within 60 days after the previous operation.

In a recent meta-analysis of 16 studies by Khajuria et al., it was found that autologous-BR is more cost-effective and is associated with better QoL compared to implant-BR [26]. However, the quality of these studies was considered poor and showed high degrees of bias. This might explain why we could not replicate the favorable results of autologous-BR over implant-BR. Other reasons for this discrepancy may be that previous cost-effectiveness studies used QALY estimates that were either gathered from a panel of experts, who imposed a large QALY difference in favor of autologous-BR, or that in some studies QALY scores based on converted scores from the condition-specific Breast-Q were used [20,30,32,36,37,45]. Outcomes that are derived from the condition-specific Breast-Q questionnaire inherently suffer from a focus-effect [38]. This is because the BREAST-Q questionnaire focusses on QoL related to breast surgery and differences in treatments are measured on that subset of QoL instead of complete health-related QoL profiles which a QALY should represent [20]. Moreover, the values used may not necessarily reflect societal preferences for health outcomes. As Matros et al. considered their outcome “Breast QALYs” they implicitly recognized that their values do not represent generic QALYs as prescribed by the guidelines of cost-effectiveness research. By using expert opinions and condition specific measures instead of using validated generic utility measures based on societal preferences, previous studies may have magnified the differences in QoL outcomes between the different surgical treatments, making these so-called “QALY” outcomes unsuitable for comparison with other medical interventions. This overvaluation of effects may have allowed to off-set the high costs, which are associated with autologous-BR procedures. However, after using an appropriate generic QALY measure as the EQ-5D, the large beneficial effect of autologous-BR seems to disappear [11,39].

Many studies on BR outcomes suffer from risk of bias, design problems and substantial discrepancies in reported complications [26,40]. The lack of reliable, comparable and comprehensive data on complications and resource use in treatment pathways for BR, BCT and mastectomy motivated us to perform a large empirical cost-utility analysis (i.e. that is a cost per QALY analysis) using real patient data instead of performing a simulated decision-making model such as a Markov-model. A consequence of this choice was a more limited time-horizon for the analysis.

For autologous-BR to become cost-effective compared to implant-BR, its QALY gain needs to improve. One reason we believe the QALY gain of autologous-BR in real-life lags behind the expected value by physicians, is that complications of autologous-BR procedures, which occur relatively frequently, have a large and long-lasting negative impact on the QoL of patients [11,40]. Autologous-BR complications are at the same time associated with very high additional absolute and relative costs, with a €10,009 (80%) increase in plastic surgery costs compared to an uneventful course. This suggests that a potentially effective way to improve the cost-effectiveness of autologous-BR techniques would be a reduction of the incidence of complications. The scenario sensitivity analysis showed that reductions in complication rates can quickly bring the ICER of autologous-BR down from the very high value we found in the present study to more acceptable levels, ranging from an estimated €80,000/QALY after a 40% reduction in complication rates to even below €50,000/QALY following a 60% reduction. This scenario analysis showed that large reductions in complication rates of autologous-BR can potentially allow autologous-BR to attain acceptable cost-effectiveness levels compared to its most important alternative, implant-BR. Further studies on patient selection and risk factor reduction will be required to study the possibilities to reach such reductions in complication rates following autologous-BR.

Limitations

The current study was not a randomized controlled trial (RCT) but an observational study, which included all patients who had been treated during the study period and who fulfilled the inclusion criteria. This means there were differences in pre-treatment characteristics between the patients. The effects of pre-treatment differences were in part reduced, as we used adjusted quality of life weights (utilities) to estimate the QALY outcomes. These quality of life weights came from a previous study that used propensity score matching to adjust for pre-treatment differences between the treatment groups. But obviously quality of life was not the only factor which may have been influenced by the pre-treatment differences. The health resource use/costs aspect of the CEA may also have been influenced by factors such as age of the patient, tumor stage, existing comorbidities and other factors. Although we would have wanted to correct for such factors, the current methodology unfortunately did not allow us to do so. This means that the results should be interpreted with caution. However, we presume that the imbalance between the groups may have mainly led to relatively older and more fragile patients with more comorbidities in the mastectomy and BCT groups, which may have lowered the aggregated QALYs and raised the costs of these two treatment groups. This means that if we would have had the opportunity to correct factors such as age and comorbidity, this would likely have further decreased the cost-effectiveness of implant-BR and autologous-BR compared to BCT and mastectomy.

The current study only included costs from the intramural healthcare provider perspective instead of also including societal costs that the patient and its surroundings may have incurred as a consequence of the disease and its treatment (e.g., productivity loss, transportation, visits to the GP, physiotherapist, psychologist, and also second opinions at other hospitals or visits to emergency rooms outside of the studied hospitals). All these aspects together may have led to an underestimation of the total incurred costs related to the different treatment pathways. Further research should investigate whether including the additional costs from the societal perspective would change the relative cost-effectiveness outcomes.

The results of the current study are based on the Dutch healthcare system and may not be directly extrapolated to healthcare systems of other countries. However, we believe that although the absolute costs may not be identical, the results of this study do provide a good insight in the relative costs of the different treatment pathways.

Clinical implications

Although this was a cost-effectiveness study, the results have implications for clinical decision-making. First of all, it seems that compared to mastectomy, BCT and BR produce more QALYs. Consequently, if mastectomy is not the only option, patients should be informed that BCT and BR on average provide more benefits. When considering autologous-BR, patients should be informed that if a postoperative complication occurs, for which the risk is relatively high [34], it has long-lasting negative effects on QoL and is requires a substantial amount of additional medical care. If the patient is risk averse in considering the trade-off between the expected outcomes and the risk of complications, autologous-BR would not be the preferred option. Finally, if BCT is feasible, it is a good starting point of any clinical deliberation between surgical options, as its oncological outcomes are comparable to mastectomy [41], its QoL outcomes are comparable to BR and surgery is more straightforward with the least complications.

Conclusions

The results of the present study suggest that mastectomy provides the least benefits for patients. When the other surgical treatment options are considered, the full-incremental cost-effectiveness analysis showed BCT was less expensive and showed a marginally more favorable QoL, thereby dominating over both implant-BR and autologous-BR. BCT had an ICER of €17,246/QALY compared to mastectomy. QoL and costs of autologous-BR seem to be strongly affected by the relatively high occurrence of complications, which prevented autologous-BR from reaching acceptable cost-effectiveness levels compared to implant-BR and BCT. If reconstruction of the breast mound following mastectomy is considered, implant-BR seems to be the most cost-effective technique. As far as cost-effectiveness is concerned, BCT seems the best surgical treatment of choice for breast cancer patients.

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Statement of institutional review board approval

The study protocol was reviewed and approved by the Medical Ethics Committee of the Erasmus MC (MEC-2015-273).

The data that support the findings of this study are not publicly available. Data are available from the authors upon reasonable request. The study was not preregistered in an independent, institutional registry.

CRediT authorship contribution statement

Casimir A.E. Kouwenberg: Conceptualization, Writing - original draft, Writing – review & editing, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis. **Marc A.M. Mureau:** Conceptualization, Writing – review & editing, Study design, Data acquisition, Data analysis and interpretation. **Leonieke W. Kranenburg:** Conceptualization, Writing – review & editing, Study design, Quality control of data and algorithms, Data analysis and interpretation. **Hinne Rakhorst:** Writing – review & editing, Data acquisition. **Daniëlle de Leeuw:** Writing – review & editing, Data acquisition. **Taco M.A.L. Klem:** Writing – review & editing, Data acquisition. **Linetta B. Koppert:** Data acquisition, Manuscript review. **Isaac Corro Ramos:** Formal analysis, Data curation, Writing – review & editing, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis. **Jan J. Busschbach:** Conceptualization, Writing – review & editing, Study design, Data analysis and interpretation.

Declaration of competing interest

Prof. Dr. Busschbach is a member of the non-profit EuroQoL Group and receives financial compensation for managerial activities for the group. For the remaining authors, none were declared.

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Appendix. Methods

Defining the cohort for analysis

This multicenter observational cohort study included all patients who had undergone surgical breast cancer treatment in one of the participating hospitals in the period between January 1st, 2005 and January 1st, 2017. Cohorts were defined on an intention-to-treat basis where patients had either undergone BCS or mastectomy. Medical intervention billing coding was used to identify the procedure a patient had received and to which cohort the patient belonged.

A 10-year time-horizon was chosen, as costs for BR are incurred over a longer period of time. Costs were assessed from a healthcare provider perspective based on Dutch unit costs. However, the healthcare provider perspective does not cover all societal costs. For instance, productivity loss (work) and small out-of-pocket costs, like travel costs were not included. This was because in this investigation it was not possible to collect such data from hospital registers, and retrospectively collecting such data retrospectively over a 10-year period is cumbersome.

Because an intention-to-treat design was used, if post-mastectomy BR had been performed, the type of the first BR procedure defined the cohort. For example, if a patient initially had undergone an implant-BR, but due to complications this BR was converted to an autologous-BR, this patient remained in the implant-BR cohort. All autologous-BR patients had undergone a breast reconstruction using free tissue transfer (almost exclusively DIEP-flaps). Patients who had undergone novel and more rare types of BR as their first BR (such as a latissimus dorsi or pedicled TRAM-flap) were excluded from the analyses, as they were considered out of the scope of the current cost-effectiveness analysis (CEA).

In the Netherlands, autologous-BR is performed in a limited number of hospitals. This means that a large proportion of patients had received their oncological breast cancer treatment at a different hospital than one of the participating hospitals and that they had been referred to receive their autologous-BR at a later stage in one of the participating centers. Consequently, the data on the oncological surgery part of their treatment was not available for these patients. Multiple imputation techniques were therefore used to address the missing surgery data [27,42]. These patients by definition had a delayed BR and for them the mean time between mastectomy and autologous-BR was used, which could be calculated for cases that had received their oncological surgery treatment at one of the participating centers.

Resource use and costs

Costs of Surgical interventions

A costing model used previously for a costing-study by Damen et al. was further developed and updated to reflect 2018 prices for the current study [31,43]. Surgical interventions were expected to be one of the main cost drivers. For this reason, we put emphasis on precise calculation of these costs. For instance, the costs for an operating room (OR) were calculated on a per minute basis for the surgeon, anesthesiologist, supporting personnel, and OR-related costs. In addition, a base fee for the OR, and breast implant costs, if used, were also added. The hospital operation registration system was used to score which surgical procedures were performed, who performed the operation, as well as details on the start and end of the operation.

After surgery, as time goes by, it becomes increasingly complicated to attribute a given medical procedure to a complication of the surgical procedure of interest. This is impeded by the often-compendious labelling of events in the hospital registers. Therefore, the occurrence of a surgical complication that required reoperation was defined as the occurrence of an additional operative procedure within 60 days. Even though long-term complications were not formally identified, the costs incurred by such complications were included in the analysis, as all relevant treatment costs during the follow-up period were included.

Costs of Radiotherapy

Because radiotherapeutic treatment in the Netherlands is centralized in a limited number of hospitals, some patients had received their radiotherapeutic treatment outside the group of five hospitals in this investigation. Therefore, costs data related to radiotherapeutic treatment could not be obtained for all patients from the hospital administrative records of four of the five participating hospitals. Consequently, radiotherapeutic resource use per patient was obtained from the Netherlands Cancer Registry upon request [44]. Unit costs for radiotherapeutic treatment were calculated as the weighted average of the resource use and reference costs for BC patients in the hospital for which these records were available. These unit costs were subsequently multiplied by the resource use as registered in the Netherlands Cancer Registry. For comparability purposes this method was employed for all patients. All BCS patients were assumed to have received radiotherapy, which is standard of care in the Netherlands.

Other Costs

Use of other cost resources were collected from the hospital administrative records. Three main categories of resources were defined: outpatient related resources, admission related resources and diagnostics related resources. The total costs for each patient were calculated by multiplying the resource use by the appropriate unit costs, standardized to 2018 prices. The Statistics Netherlands (CBS) inflation tool was used to adjust prices of all resources, also of the surgical interventions and radiotherapy [43]. Multiple sources were used to obtain unit costs, in order of preference: reference costs for medical resources as published by the National Health Care Institute of the Netherlands (Zorginstituut Nederland), national costs guideline for diagnostic procedures, cost prices provided by business information departments of respective hospitals, reimbursement fees of healthcare insurers [23,24].

Health outcomes

Patients' health states were defined on a per year basis based on the last operation they had undergone. Four health states were defined: mastectomy, BCT, implant-BR and autologous-BR. In order to be able to associate these four health states with QALY values, the EQ-5D-5L outcomes of our previous study were used, which were controlled for differences in pre-treatment patient characteristics [11]. The utility values and their 95% confidence intervals that were used from this study were respectively, BCT 0.844 (CI: 0.829–0.859), mastectomy 0.805 (CI: 0.787–0.823), autologous-BR 0.849 (CI: 0.828–0.871), implant-BR 0.850 (CI: 0.823–0.877) [11]. The QALY weights provided by the EQ-5D-5L where based on Dutch societal values [45]. To account for the variance in health utility outcomes over time and between patients, all health state utilities were drawn randomly from a beta distribution of health state utility values specific for the respective treatment group.

Missing data and censoring

A complete follow-up period of 10 years was not available for all patients because of the continued inclusion in the cohort. This leads to right censoring of the cost and health utility data for these patients. The missing data were addressed according to the guideline "A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomized Controlled Trials" by Faria et al. using multiple imputation with chained equations using predictive mean matching (MI-PMM) from within the respective treatment arm [27]. This approach recognizes uncertainty associated with missing data and subsequent estimated parameters in the imputation model and is also appropriate for cost and utility data that is non-normally distributed [27,42]. To facilitate MI-PMM, costs categories and health state data were aggregated in incremental segments of 1-year follow-up after which the imputation procedure was performed using the ICE program in Stata 14 on Mac OSX. Cost data were log-transformed as is recommended when performing MI-PMM in datasets with large amounts of missing data and zero-inflated cost data [42]. Due to lack of variance in individual cost categories in later years of the follow-up because too many patients had not incurred any costs at all, aggregation of the costs categories "outpatient", "admission" and "diagnostics" was performed where required to obtain a robust model. Fifty imputation datasets were created with predictive mean matching for each variable and a random seed of 10. Table Appendix 1 shows all variables included in the MI-PMM model and their respective missing values for all treatment groups combined and specified per ITT treatment group.

Cost-effectiveness and sensitivity analysis

Total costs for each cost category, total costs for both the surgical oncology and plastic surgery departments, overall total costs and total QALYs aggregated (over time) were calculated for each patient in the imputed datasets. Costs and QALYs were discounted with a rate of 4% and 1.5% per year, respectively, in accordance with the national guideline on CEA [24]. Discounting accounts for the economic theory that effects and costs become of less value to an individual the further away in the future they are [20]. The main measure of cost-effectiveness is the incremental cost-effectiveness ratio (ICER), calculated as the difference in mean costs per patient divided by the difference in mean QALYs per patient over the 10-year period. In addition to a full-incremental analysis in which all available options were compared to another, also pairwise comparisons were performed.

The MIM2 program in Stata was used for basic analysis of the imputed datasets using Rubin's rules [46]. Furthermore, three scenario sensitivity analyses were performed: 1) 20% higher and lower OR costs were investigated to illustrate the effects of any differences in this main costs driver. 2) A scenario which assumed that all implant-BR patients needed to undergo one re-operation in year 10 for implant replacement and for which all associated additional costs were taken into account. The reason for investigating this scenario was that implant-BR is associated with a relatively high risk of additional operations in the long-term due to for example capsular contracture or implant rupture [26,40,47]. The costs of these additional operations have often been mentioned as closing the costs gap between autologous-BR and implant-BR, which would eventually lead to break-even costs in the long-term [34]. 3) The effects of a reduction of the complication rate of autologous-BR on QoL as well as on costs were investigated in a weighted average fashion. This scenario illustrates possible effects of differences and future improvements in quality of care.

Appendix table 1
Overview of variables in MI-PMM-model with their percentage of missing values

Percent Missing	Overall	MAS	BCS	IBR	ABR
PAT_UID	0	0	0	0	0
ITT	0	0	0	0	0
age_start_treatment	0	0	0	0	0
Hospital_ID	0	0	0	0	0
prem_OR	0	0	0	0	0
Rtx_treatments	17	15	11	14	82
t1_SUR_cmORs	5	0	0	0	80
t2_SUR_cmORs	9	4	4	4	81
t3_SUR_cmORs	18	11	17	11	83
t4_SUR_cmORs	26	18	26	24	85
t5_SUR_cmORs	35	26	36	34	87
t6_SUR_cmORs	43	34	45	46	89
t7_SUR_cmORs	52	42	56	57	90
t8_SUR_cmORs	60	51	64	67	92
t9_SUR_cmORs	69	60	74	76	94
t10_SUR_cmORs	78	70	83	84	96
t1_PLC_cmORs	0	0	0	0	0
t2_PLC_cmORs	4	4	4	4	1
t3_PLC_cmORs	13	11	17	11	3
t4_PLC_cmORs	21	18	26	24	11
t5_PLC_cmORs	31	26	36	34	22
t6_PLC_cmORs	40	34	45	46	31
t7_PLC_cmORs	49	42	56	57	39
t8_PLC_cmORs	57	51	64	67	48
t9_PLC_cmORs	67	60	74	76	57
t10_PLC_cmORs	76	70	83	84	65
SUR_t4_total_cost_care_pathway	24	18	26	24	62
SUR_t5_total_cost_care_pathway	33	26	36	34	66
SUR_t6_total_cost_care_pathway	42	34	45	46	69
SUR_t7_total_cost_care_pathway	51	42	56	57	73
SUR_t8_total_cost_care_pathway	59	51	64	67	78
SUR_t9_total_cost_care_pathway	68	60	74	76	82
SUR_t10_total_cost_care_pathway	77	70	83	84	86
PLC_t9_total_cost_care_pathway	90	93	94	76	57
PLC_t10_total_cost_care_pathway	93	95	96	84	65
SUR_t1_c_gr_outpatient	5	0	0	0	80
SUR_t2_c_gr_outpatient	9	4	4	4	81
SUR_t3_c_gr_outpatient	18	11	17	11	83
PLC_t1_c_gr_outpatient	68	80	77	0	0
PLC_t2_c_gr_outpatient	69	81	78	4	1
PLC_t3_c_gr_outpatient	72	83	81	11	3
PLC_t4_c_gr_outpatient	75	84	83	24	11
PLC_t5_c_gr_outpatient	78	86	86	34	22
PLC_t6_c_gr_outpatient	81	88	89	46	31
PLC_t7_c_gr_outpatient	85	89	91	57	39
PLC_t8_c_gr_outpatient	87	91	92	67	48
SUR_t1_c_gr_admission	5	0	0	0	80
SUR_t2_c_gr_admission	9	4	4	4	81
SUR_t3_c_gr_admission	18	11	17	11	83
PLC_t1_c_gr_admission	68	80	77	0	0
PLC_t2_c_gr_admission	69	81	78	4	1
PLC_t3_c_gr_admission	72	83	81	11	3
PLC_t4_c_gr_admission	75	84	83	24	11
PLC_t5_c_gr_admission	78	86	86	34	22
PLC_t6_c_gr_admission	81	88	89	46	31
PLC_t7_c_gr_admission	85	89	91	57	39
PLC_t8_c_gr_admission	87	91	92	67	48
SUR_t1_total_c_gr_diagnostics	5	0	0	0	80
SUR_t2_total_c_gr_diagnostics	9	4	4	4	81
SUR_t3_total_c_gr_diagnostics	18	11	17	11	83
PLC_t1_total_c_gr_diagnostics	68	80	77	0	0
PLC_t2_total_c_gr_diagnostics	69	81	78	4	1
PLC_t3_total_c_gr_diagnostics	72	83	81	11	3
PLC_t4_total_c_gr_diagnostics	75	84	83	24	11
PLC_t5_total_c_gr_diagnostics	78	86	86	34	22
PLC_t6_total_c_gr_diagnostics	81	88	89	46	31
PLC_t7_total_c_gr_diagnostics	85	89	91	57	39
PLC_t8_total_c_gr_diagnostics	87	91	92	67	48
t1_HS	0	0	0	0	0
t2_HS	4	4	4	4	1
t3_HS	13	11	17	11	3
t4_HS	21	18	26	24	11
t5_HS	31	26	36	34	22

(*continued on next page*)

Appendix table 1 (*continued*)

Percent Missing	Overall	MAS	BCS	IBR	ABR
t6_HS	40	34	45	46	31
t7_HS	49	42	56	57	39
t8_HS	57	51	64	67	48
t9_HS	67	60	74	76	57
t10_HS	76	70	83	84	65

MAS: mastectomy without breast reconstruction; *BCT*: breast conserving therapy; *IBR*: mastectomy with implant breast reconstruction; *ABR*: mastectomy with autologous breast reconstruction; *SUR*: surgical oncology; *PLC*: plastic surgery; *PAT_UID*: unique patient identifier; *ITT*: intention to treat treatment group; *age_start_treatment*: age at start of treatment; *Hospital_ID*: hospital identifier; *prem_OR*: number of complications requiring reoperation; *Rtx_treatments*: number of radiotherapy therapies; *cmOR*: operation related costs; *outpatient*: outpatient related costs; *admission*: admission related costs; *diagnostics*: diagnostics related costs; *tx*: variable aggregated for year x of follow-up; *total_cost_care_pathway*: aggregation of the costs categories outpatient, admission and diagnostics due to lack of variance in individual categories; *HS*: health state utility value.

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