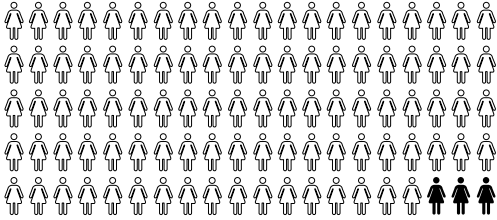


Ultrasound-guided surgery



3%

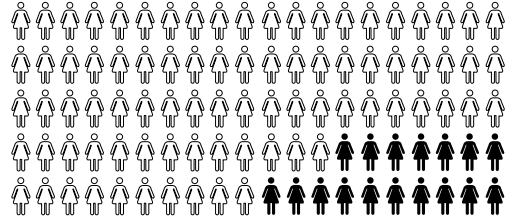
of patients had tumour-involved margins



CRR=1

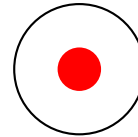
the ideal amount of healthy breast tissue resection

Palpation-guided surgery



17%

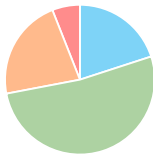
of patients had tumour-involved margins



CRR=1.7

1.7 times the ideal amount of healthy breast tissue resection

Cosmetic Outcome



72%

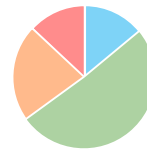
perfect
good

6%

fair
poor

90%

of women were satisfied or very satisfied with the appearance of their breast



65%

perfect
good

13%

fair
poor

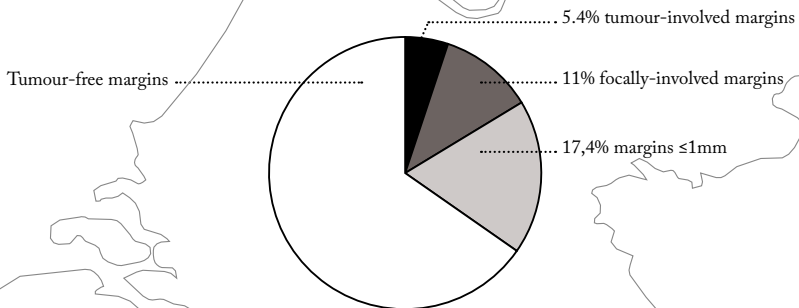
80%

of women were satisfied or very satisfied with the appearance of their breast

The Netherlands

Breast-conserving surgery was performed in 9276 patients over 2012 and 2013

Ultrasound-guided surgery could decrease healthcare costs by € 1,001,655 per year



In Dutch patients a median of 2.34 times the optimal resection volume was excised

SUMMARY

Breast cancer is the most common form of cancer in women, with an estimated worldwide incidence of 1.38 million cases per year. Due to improvements in screening, the majority of breast cancer patients today present at an early stage and the tumours seen at first presentation are relatively small (diameter <5cm).

A number of trials have been conducted to compare the efficacy of mastectomy to that of breast-conserving surgery (BCS), followed by whole breast irradiation to eradicate microscopic residual disease (also referred to as breast-conserving therapy). These trials demonstrated that the two approaches are equivalent in terms of disease-free and overall survival. Mastectomy has since declined and breast conserving therapy (BCT) is now the standard procedure for early-stage breast cancer, with 75% of breast cancer patients qualifying for BCT according to Dutch breast-cancer guidelines.

The goals of BCT are to deliver low local recurrence rates and equivalent survival rates to mastectomy, while achieving an acceptable cosmetic outcome. Despite the best surgical efforts, tumour-involved surgical margins still occur in 20-40% of all tumour excisions, leading in many cases to additional boost radiation, re-excision or even mastectomy. Nevertheless, the current 5-year survival rates after BCT for early stage breast-cancer are excellent (>95%), and local recurrence rates range from 2% to 5%.

Although an important secondary goal in BCS is to achieve a satisfactory cosmetic outcome, a factor crucial to patient satisfaction and quality of life, poor cosmetic outcomes are still observed in up to 40% of patients. Against a background of excellent survival rates, the focus of BCS is now shifting towards improving cosmetic outcomes.

Chapter 2. Ultrasound-guided surgery (USS) could potentially improve tumour-free margin rates and cosmetic outcomes of BCS for palpable breast cancer. This prospect led to the initiation of the COBALT trial in 2010, with the primary goal the comparison of ultrasound-guided surgery to the standard for palpable breast cancer, palpation-guided surgery (PGS), in terms of margin status and extent of healthy breast tissue resection.

COBALT was a randomized clinical trial that recruited patients with palpable T1-T2 invasive breast cancer between October 2010 and March 2012, in 6 medical centres in the Netherlands. Participants were randomly assigned to either USS or PGS. The primary outcomes were surgical margin involvement (classified as tumour-free, focally positive, or positive), and excess healthy tissue resection, defined by a calculated resection ratio (CRR) (derived from excision volumes and tumour diameters). A CRR of 1 indicated excision of the ideal amount of healthy breast tissue, whereas a CRR of 2 indicated excision of twice the ideal amount. In total, 134 patients were randomly assigned to USS (n = 65) or PGS (n=69). A dramatic difference in margin involvement was seen: only 2 (3%) of the 65 patients in the ultrasound-guided surgery group showed tumour-involved margins, compared to 12 (17%) of the 69 patients in the palpation-guided surgery group. USS also resulted in reduced excision volumes, 38 cc vs. 58 cc and reduced CRR, 1.0 vs. 1.7 in PGS. These findings showed that continuous intraoperative tumour visualisation with USS can deliver significantly lower rates of tumour-involved resection margins in palpable breast cancer excision, thus reducing the need for additional interventions such as re-excision, mastectomy or radiotherapy boost.

“Continuous intraoperative tumour visualisation by ultrasound-guided surgery achieves a significantly lower rate of tumour-involved resection margins during palpable breast cancer excision”

Chapter 3. The ultrasound system required for USS entails certain costs, but as shown in chapter 2, USS reduces the need for additional therapies. An economic evaluation of the COBALT trial was initiated to assess the costs and benefits of USS compared to PGS. On the cost side, resource use related to baseline treatment was taken into account (the ultrasound system) and on the benefit side resource use related to additional treatments was included (re-excision, mastectomy and the costs of hospitalisation). In terms of costs, the mean difference in costs per patient was €193, with higher costs in the USS group. On the benefit side, the mean difference in costs per patient was €349 due to additional treatments, with higher costs in the PGS group. This resulted in overall costs that were €154 lower in the USS group compared to the PGS group. We therefore conclude that the reduction in the rate of tumour-involved margins with USS compared to PGS leads to a reduction in healthcare costs.

“Ultrasound-guided surgery for palpable breast cancer leads to a reduction in healthcare costs”

Chapter 4. Despite the increasing interest in the evaluation of cosmetic outcomes following breast-conserving therapy (BCT) over recent decades, no consensus has yet been reached on the optimal approach to cosmetic evaluation. In chapter 4 we compare the strengths and weaknesses of the BCCT.core cosmetic outcome evaluation software to those of a 10-member panel from diverse backgrounds. Digital photographs of 109 consecutive patients after BCT for primary T1-T2 invasive breast cancer were evaluated for 7 items by a panel consisting of 2 breast surgeons, 2 residents, 2 laypersons and 4 plastic surgeons. All photographs were then objectively evaluated using the BCCT.core software, and an overall cosmetic outcome score was reached using a four-point Likert scale (poor, fair, good and excellent). Based on the mean BCCT.core software score, 41% of patients had fair or poor overall cosmetic results (10% poor), compared with 51% (14% poor) scored by panel evaluation. The mean overall BCCT.core scores and mean overall panel scores showed substantial agreement (weighted kappa: 0.68). By contrast, analysis of the evaluation of scar tissue revealed large discrepancies between the BCCT.core software and the panel. In conclusion, although software analysis of scar tissue shows room for improvement, overall the BCCT.core represents a valid and efficient alternative to panel evaluation.

“BCCT.core cosmetic evaluation software represents a valid and efficient alternative to panel evaluation”

Chapter 5. In light of the significant reduction in both margin involvement and excision volumes achieved by USS in the COBALT trial, this chapter describes our efforts to determine whether USS also leads to improvements in cosmetic outcome and patient satisfaction when compared to standard palpation-guided surgery (PGS).

The same 134 patients with T1-T2 invasive breast cancer included in the COBALT trial were analysed (65 USS patients and 69 PGS patients). Cosmetic outcomes were assessed by a three-member panel, by the computerized BCCT.core software and by patient self-evaluation, including evaluation of patient satisfaction. Time points for follow-up were 3, 6 and 12 months after surgery. Overall cosmetic outcome and patient satisfaction were scored on a 4-point Likert scale (poor, fair, good and excellent). USS achieved better cosmetic outcomes, with 20% excellent overall and only 6% rated as poor, whereas 14% of PGS outcomes were rated excellent and 13% as poor. USS also showed consistently lower odds for poorer cosmetic outcomes (OR=0.55, p=0.067) than PGS. The chance of having a worse outcome was significantly increased by a larger lumpectomy volume; a volume >40cc showed odds 2.78 times higher for a worse outcome than a volume ≤40cc. USS also resulted in a higher patient satisfaction compared with PGS.

“USS delivers better overall cosmetic outcomes and patient satisfaction than PGS”

Chapter 6. As demonstrated in the COBALT trial, USS can significantly improve margin involvement rates and the extent of healthy breast tissue resection. However, objective results on margin involvement and resection of healthy breast tissue during BCS are currently lacking in the Netherlands. Therefore, this chapter describes the assessment of margin status in relation to the amount of healthy breast tissue resected in breast-conserving surgery (BCS) on a nationwide scale. Using PALGA (a national network and registry of histology and cytopathology in the Netherlands), we selected all patients who underwent BCS for primary invasive carcinomas during 2012-13 (10,058 excerpts). Pathology excerpts (n=9276) were then analysed for a range of criteria including oncological margin status and distance to closest margin, specimen weight/volume, greatest tumour diameter, and with or without use of a localisation method. Calculated resection ratios (CRR) were assessed to determine excess healthy breast tissue resection. Margins for invasive carcinoma and in situ carcinoma combined were tumour-involved in 498 cases (5.4%) and focally-involved in 1021 cases (11.0%). Unsatisfactory resections, including (focally) involved margins and margins ≤ 1 mm, were reported in 33.8% of cases. The median lumpectomy volume was 46 cc (range 1 – 807 cc; SD 49.18) and median CRR 2.32 (range 0.10 – 104.17; SD 3.23), indicating the excision of 2.3 times the optimal resection volume. This unacceptably high rate of tumour-involved margins, in addition to margins ≤ 1 mm in one third of all patients, occurs at the expense of healthy breast tissue resection and thus potentially carries a risk of high rates of cosmetic failure.

“In the Netherlands, there is a need for improvement in the current breast-conserving surgical procedures that aim to decrease tumour-involved margin rates while reducing the amount of healthy breast tissue resected”

Chapter 7. Referred to as oncoplastic breast surgery (OPBS), new surgical approaches combine oncological resection of breast cancer with plastic surgery techniques in a single procedure. In this systematic review we evaluated the oncological and cosmetic outcomes of OPBS. The secondary objectives were assessment of morbidity, quality of life and applied algorithms. Using specific inclusion and exclusion criteria to analyse 2090 abstracts on the topic of OPBS, published between 2000 and 2011, the authors evaluated each study with respect to design and outcomes. A total of 88 articles were identified for potential inclusion and reviewed in detail by the lead authors. No randomised controlled trials were identified. Eleven prospective observational or comparative studies fulfilled inclusion criteria and were selected. In these studies, 80% to 93% of the tumours were invasive. Tumour-free resection margins were observed in 78% to 93%, resulting in a 3% to 16% mastectomy rate. Local recurrence was observed in 0% to 7% of the patients. Good cosmetic outcome was obtained in 84% to 89% of patients. However, most studies showed significant weaknesses such as lack of robust design which, together with important methodological shortcomings, negatively influenced generalizability. Given the increasing importance and application of OPBS, there is a pressing need for robust comparative studies, including both randomized controlled trials and well-designed, multicentre prospective longitudinal studies.

“This systematic review reveals that current evidence supporting the efficacy of oncoplastic breast-conserving surgery is derived from poorly-designed and underpowered studies”