

Persistent pain, sensory disturbances and functional impairment after immediate or delayed axillary lymph node dissection

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Abstract

Background: Patients treated with 2-step axillary lymph node dissection (ALND) may be at increased risk of nerve damage due to more challenging surgery than an ALND immediately after a sentinel lymph node biopsy (SLNB), and thus more at risk for persistent pain after breast cancer treatment (PPBCT). The aim of this study was to examine PPBCT, sensory disturbances and functional impairment in patients treated with a 2-step ALND compared to patients with an SLNB followed by an immediate ALND, and patients with ALND without a prior SLNB.

Methods: The study is a cross-sectional questionnaire study, comparing 2847 women treated with ALND in Denmark in 2005–2008. 196 patients treated with a 2-step ALND were compared with 1558 patients treated with an ALND after SLNB and 1093 with an ALND without a prior SLNB.

Results: Overall prevalence of PPBCT and sensory disturbances was high, with about 55% reporting PPBCT and 77% reporting sensory disturbances in all groups. No differences were found between the groups on prevalence and intensity of PPBCT ($p = 0.92$), sensory disturbances ($p = 0.32$), and functional consequences ($p = 0.35$).

Conclusions: A 2-step ALND does not modify the risk of developing PPBCT compared to an immediate ALND.

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Keywords: Breast cancer; Persistent pain; Axillary lymph node dissection; Neuropathy

Introduction

Persistent pain after breast cancer treatment (PPBCT) is a considerable clinical problem affecting between 25 and 60% of the patients, depending on treatment.¹ Several risk factors have been proposed, among them nerve damage on basis of surgery and radiotherapy.² Axillary lymph node dissection (ALND) was in a recent review of the PPBCT literature shown to be consistently associated with a higher prevalence and intensity of PPBCT and sensory disturbances compared to sentinel lymph node biopsy (SLNB),² suggesting damage of the intercostobrachial nerve (ICBN) as a potential pathophysiological mechanism. Among women without suspicion of metastatic spread to the

axillary lymph nodes, intraoperative frozen sections of the excised sentinel nodes are standard care, from which the decision to make an immediate ALND is based. In 10–20% of frozen sections performed during SLNB there is failure to identify malignancy that is subsequently discovered during postoperative histopathological examination.³ These patients are then generally offered a delayed ALND, called a 2-step ALND. A 2-step ALND is more challenging to perform due to fibrosis in the surgical field, and thus we hypothesized that the surgical trauma would be more pronounced and the risk of damage of the ICBN would be increased, consequently with an increased risk of developing PPBCT. The aim of this study was to examine the risk of PPBCT, pain intensity, sensory disturbances and functional impairment in patients undergoing a 2-step ALND compared to patients with an SLNB followed by an immediate ALND, and patients with ALND without a prior SLNB.

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Methods

Study design and setting

The study is a cross sectional questionnaire study including patients from 2 cohorts treated for breast cancer in Denmark between 2005–2006¹ and 2007–2008⁴ respectively. The studies of the two cohorts were done with an identical set-up and questionnaire.¹ A study comparing the two cohorts, showed no differences in PPBCT, sensory disturbances in the area of surgery or functional impairment.⁴ Data collection was done at 2 occasions, to ensure a comparable time of follow-up, at Rigshospitalet, Copenhagen, Denmark.

Participants

Patients were identified in Danish Breast Cancer Cooperative group's (DBCG) database. The DBCG database prospectively collects data on treatment and disease characteristics.⁵ Inclusion criteria in both cohorts were: women aged between 18 and 69 years, treated for primary operable breast cancer including ALND. Both cohorts were nationwide. For the 2005–2006 cohort, all patients following a protocol treatment programme were eligible for inclusion, while the 2007–2008 cohort was restricted to patients allocated to adjuvant chemotherapy. Exclusion criteria for both cohorts were contraindication to treatment according to the DBCG treatment protocol, recurrence or new primary breast cancer, other malignancy, emigration or reconstructive or cosmetic surgery. Data on patients who had received reconstructive surgery were acquired from the Danish National Patient Registry (NPR),⁶ where all treatment in the Danish health care system is reported, as a prerequisite for funding.

Identification of patients treated with a 2-step procedure

Data on surgery, adjuvant treatment and follow-up were provided from the DBCG. Identification of patients receiving a 2-step ALND was done by combining data from the DBCG register and NPR. In the DBCG database only the date of the first procedure is registered, whereas in the NPR, exact dates including subsequent procedures are registered for each procedure. We allowed up to one week discordance in dates of SLNB between the NPR and the DBCG databases, allowing for registration errors. And thus a 2-step procedure was defined as patients having an ALND between 7 and 60 days after an SLNB on the same side. The study has been approved by the Danish Data Protection Agency (J.nr 2007-58-0015), and by the National Board of Health (J.nr. 7-505-29-1538/1).

Treatment

The surgical and adjuvant treatment was standardized according to DBCG guidelines in both cohorts; surgery

included either mastectomy or breast conserving surgery (BCS) with either SLNB or ALND levels I and II. Radiotherapy and chemotherapy were offered to patients according to risk profile. Patients treated between 2005 and 2006 received chemotherapy with cyclophosphamide, epirubicin and fluoruracil according to the DBCG04 protocol, and the 2007–2008 cohort received cyclophosphamide and epirubicin followed by docetaxel according to the DBCG07 protocol. Patients with hormone receptor positive tumor were offered endocrine treatment. Both protocols were based on the recommendation from the International Expert Consensus on Primary Therapy of Early Breast Cancer in 2003⁷ respectively 2005.⁸

Outcomes

The study questionnaire developed for the assessment of PPBCT, sensory disturbances and functional impairment in the 2005–2006 cohort^{1,9} was used in both cohorts. The primary outcome was the risk of PPBCT associated to a 2-step ALND compared to an immediate ALND, expressed as an odds ratio. PPBCT was defined as presence of pain in the breast, side of chest, axilla or arm on the operated side more than 12 months after surgery. Secondary outcomes were intensity of pain in the 4 localizations, sensory disturbances in the breast, side of chest, axilla and the arm on the operated side, and functional impairment. Questions addressing prevalence of pain were assessed dichotomously with yes/no questions. Patients were then asked systematically to specify pain according localization and intensity. Intensity was assessed on a 1–10 numerical rating scale (NRS) and reported as light pain NRS 1–3, moderate pain NRS 4–7 and severe pain NRS 8–10. Sensory disturbances were assessed by a dichotomous yes/no question, and the localization was specified. Functional impairment was assessed by asking whether or not the patient have had to give up any activities because of the treatment.

Statistics

The analysis of data was made by the DBCG data center. Multivariate logistic regression models were applied to evaluate influence of the three groups adjusted for available risk factors. Using Proc Logistic in the SAS version 9.2 (SAS Institute, Cary, NC, USA), the following factors were included: type of breast surgery (BCS vs. mastectomy), type of surgery in axilla ALND vs. SLNB, radiotherapy (breast radiotherapy (BRT)/anterior thoracic radiotherapy (ATRt) + locoregional radiotherapy (LRRT) vs. BRT vs. none), year of surgery (2005 vs. 2006 and 2007 vs. 2008), age, chemotherapy (CEF/CE + T vs. none) endocrine therapy (tamoxifen or aromatase inhibitor vs. none). Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated, and Wald χ^2 -test was used to test the overall significance of each parameter. All OR noted in the text are adjusted OR. Associations between

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