A Double-blind Randomized Trial of Wound and Intercostal Space Infiltration with Ropivacaine during Breast Cancer Surgery

Effects on Chronic Postoperative Pain

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ABSTRACT

Background: The efficacy of local anesthetic wound infiltration for the treatment of acute and chronic postoperative pain is controversial and there are no detailed studies. The primary objective of this study was to evaluate the influence of ropivacaine wound infiltration on chronic pain after breast surgery.

Methods: In this prospective, randomized, double-blind, parallel-group, placebo-controlled study, 236 patients scheduled for breast cancer surgery were randomized (1:1) to receive ropivacaine or placebo infiltration of the wound, the second and third intercostal spaces and the humeral insertion of major pectoralis. Acute pain, analgesic consumption, nausea and vomiting were assessed every 30 min for 2 h in the postanesthesia care unit and every 6 h for 48 h. Chronic pain was evaluated 3 months, 6 months, and 1 yr after surgery by the brief pain inventory, neuropathic pain, and anxiety and depression questionnaires.

Results: Ropivacaine wound infiltration significantly decreased immediate postoperative pain for the first 90 min, but did not decrease chronic pain at 3 months (primary endpoint), or at 6 and 12 months postoperatively. At 3 months, the incidence of chronic pain was 33% and 27% (P = 0.37) in the ropivacaine and placebo groups, respectively. During follow-up, brief pain inventory, neuropathic pain, and anxiety increased over time in both groups (P < 0.001) while depression remained stable. No complications occurred.

Conclusion: This multicenter, prospective study shows that ropivacaine wound infiltration after breast cancer surgery decreased immediate postoperative pain but did not decrease chronic pain at 3, 6, and 12 months postoperatively.

What We Already Know about This Topic

• There is an association between severity of acute pain after surgery and likelihood of chronic pain, yet whether these are causally related is not known

What This Article Tells Us That Is New

• In 236 women undergoing breast surgery for cancer, wound infiltration with ropivacaine reduced postoperative pain for the first 90 min after surgery, but did not reduce the incidence or severity of pain 3–12 months later

Breast cancer affects nearly 10% of all women, and is the most common type of cancer identified in women in western countries. Early detection and treatment have led to increased survival. With the increasingly prolonged hospital anxiety and depression, and neuropathic pain questionnaires.

Results: Ropivacaine wound infiltration significantly decreased immediate postoperative pain for the first 90 min, but did not decrease chronic pain at 3 months (primary endpoint), or at 6 and 12 months postoperatively. At 3 months, the incidence of chronic pain was 33% and 27% (P = 0.37) in the ropivacaine and placebo groups, respectively. During follow-up, brief pain inventory, neuropathic pain, and anxiety increased over time in both groups (P < 0.001) while depression remained stable. No complications occurred.

Conclusion: This multicenter, prospective study shows that ropivacaine wound infiltration after breast cancer surgery decreased immediate postoperative pain but did not decrease chronic pain at 3, 6, and 12 months postoperatively.
survival of breast cancer patients, chronic postoperative pain has therefore become an important issue.

Acute pain after breast surgery is moderate and depends on the type of surgery, ranging from simple lumpectomy to mastectomy with axillary node dissection. However, the estimated prevalence of chronic pain in the literature is between 20 and 65%. Chronic pain has a neuropathic component and has been reported to occur in various areas: the chest wall, breast, scar, axilla, and medial upper arm or shoulder.

Several predictive factors, related to both the patient and surgical factors, have been identified for chronic postoperative pain. Preoperative pain sensitivity, the presence of pain before surgery, acute postoperative pain, and analgesic consumption are strong predictors of persistent pain after surgery. Postoperative loco-regional analgesia is one of the multimodal strategies used to prevent chronic pain and reduce opioid consumption and side effects. Other predictive factors include anxiety, psychosocial factors, young age (< 40 yr), type of surgery, intercostobrachial nerve damage, adjuvant radiation therapy, or chemotherapy.

Adequate and effective pain relief during the perioperative period may prevent and reduce chronic pain. Postoperative loco-regional analgesia is one of the multimodal pain relief strategies used to prevent chronic pain and reduce opioid consumption and side effects.

However, the efficacy of local anesthetic wound infiltration for the treatment of acute pain after breast surgery is controversial. The effect of local anesthetic instillation on chronic pain has been evaluated, and seems to be significantly effective at 3 months but not at 6 months. The authors suggested that larger clinical trials were necessary. Therefore, we conducted an extensive study in a homogeneous population on the effect of deep wound infiltration with ropivacaine on acute and chronic pain as well as on factors of comorbidity, such as anxiety and depression after breast cancer surgery.

The primary objective of this study was to address the question: Does wound infiltration influence the incidence of chronic pain evaluated by a score of three or more on item five (average pain) of the brief pain inventory (BPI) at 3 months after breast surgery?

The secondary objectives were to assess the following: acute postoperative pain at rest or during mobilization, the consumption of analgesics, nausea and vomiting every 30 min for 2 h in the postanesthesia care unit (PACU) and every 6 h for 48 h after surgery. Chronic pain was evaluated 3 months, 6 months, and 1 yr after surgery by the BPI, hospital anxiety and depression (HAD), and neuropathic pain (DN4) questionnaires.

Materials and Methods

Population
Four hospitals (cancer centers) participated in this prospective, randomized (1:1), double-blind, parallel-group, placebo-controlled study to evaluate the effect of ropivacaine infiltration on postoperative pain in patients undergoing breast cancer surgery. Patients were recruited from a surgical ward during the preoperative visit.

Inclusion Criteria. Women between the ages of 18 and 85 yr with an American Society of Anesthesiologists physical status I, II, and III and a minimum life expectancy of 2 yr, treated by conservative breast surgery with axillary lymph node dissection or radical modified mastectomy with either sentinel lymph node dissection or axillary lymph node dissection or no axillary lymph node dissection were included.

Exclusion Criteria. An occurrence of any previous cancer other than breast cancer, allergy to local anesthetics and morphine, reported history of substance abuse, pregnancy, ipsilateral breast surgery in the past 3 yr, preoperative analgesic use (12 h), severe renal, pulmonary, or hepatic dysfunction, active malignant disease, and those unable to comply with the protocol for any reason were excluded.

All patients gave their written informed consent, and the protocol (Eudra CT N° 2005-005691-32; ClinicalTrials.gov NCT N° NCT00370240) was approved by the institutional review board (Institut Curie, Saint-Cloud, France) and the study ethics review committee (Hôpital Ambroise Paré, Boulogne, France).

Randomization
A balanced block stratified randomization scheme was used for patient allocation. Stratification was performed on the basis of hospital and type of surgery (conservative or not). Patients were randomized in randomly permuted blocks of four or six patients in each stratum. Assignments were computer-generated and maintained in sequentially numbered, opaque, sealed envelopes. Patients were enrolled and informed consent was obtained at least 1 day before surgery. The study was performed under double-blind conditions. The envelope was opened in an isolated room on the day of surgery, and patients were assigned to either the placebo group or the ropivacaine group.

Treatment
On the morning of surgery and before induction of anesthesia, an operating room nurse read the results of randomization to prepare the solution of normal saline or ropivacaine in identical syringes, to be infiltrated by the surgeon. The solution was prepared in an isolated room and the nurse did not have any further contact with the patient. No other physician or nursing staff member was aware of the contents of the solution administered to each patient.

Patients were premedicated with hydroxyzine (2 mg/kg) administered orally 1 h before surgery. General anesthesia was induced with propofol (2.5 mg/kg), sufentanil (0.2 µg/kg), and atracurium or cisatracurium to facilitate orotracheal intubation. Anesthesia was maintained with 50% nitrous oxide in oxygen, sevoflurane (1–2% end-tidal concentration)
or desflurane (3–4%), and boluses of sufentanil 0.1 µg/kg as required. The patient was extubated at the end of surgery after reversal of the neuromuscular block, if necessary.

At the end of surgery, before skin suturing, the wound was completely infiltrated under blind conditions with repeated injections of the solution (3–4 ml for each injection), 3 cm along the subcutaneous and deep layers of the breast and axilla surgical incisions. Infiltrations were also performed in the second and third intercostal spaces and in the humeral insertion of the major pectoralis. Intercostal infiltrations were performed under visual control by the surgeon (3–4 ml for each injection) on the anterior edge of the serratus anterior muscle and the upper edge of the second and third rib. The ropivacaine group received 3 mg/kg of 0.375% ropivacaine (0.75% ropivacaine [AstraZeneca, London, United Kingdom] mixed with saline). All patients received the same per kilogram dose of ropivacaine regardless of the type of surgery. The placebo group received an equal volume of saline solution (0.8 ml/kg). One hour before the end of surgery, the patient received an intravenous injection of 1 g of paracetamol and 100 mg of ketoprofen ± omeprazole.

All patients were transferred to the PACU for 2 h. Consumption of analgesics (paracetamol, ketoprofen, and morphine), and nausea and vomiting were assessed at the time of transfer to the PACU, every 30 min for 2 h in the PACU and every 6 h for the first 48 h postoperatively. Pain was scored by a visual analog scale (VAS) anchored by no pain at all (score 0 cm) and worst possible pain (score 10 cm). Pain was evaluated by a nurse who was blinded to the treatment group. Acute postoperative pain at rest and after movement (elevation of the arm on the operated side) was assessed every 30 min for 2 h in the PACU and every 6 h for 48 h. All patients were administered oral analgesics for postoperative pain (paracetamol 1 g and ketoprofen 50 mg) every 6 h and rescue morphine with a patient-controlled analgesia pump for 24 h (bolus dose 1 mg on demand, lock-out interval of 5 min). Ondansetron 4 mg was administered for nausea and vomiting ± droperidol 1.25 mg every 8 h.

**Evaluation**

Patients were asked to fill in questionnaires at inclusion, and at 3 months, 6 months, and 1 yr after surgery evaluating chronic pain (BPI),26 anxiety-depression (HAD),27 neuropathic pain (DN4),28 consumption of analgesics, and comorbidities (lymphedema). The BPI is a multidimensional pain assessment tool which includes, pain intensity, pain’s interference with functions (seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep), and finally the experience of pain which is the consequence of pain intensity and pain interference.

Data on demographics and the history of cancer included age, body mass index, patient satisfaction, breast cancer site, adjuvant therapy, and cancer status at follow-up.

Because toxicity was not expected with ropivacaine in this study (Phase 4 study with safe doses of ropivacaine), the trial was not assessed by an independent data safety monitoring board.

**Statistical Analysis**

At 3 months, the estimated incidence of chronic pain was 40% in the control group. The number of patients included was calculated to obtain a 20% difference between the two groups (50% reduction of the incidence of chronic pain from 40 to 20%). A population of 216 patients were required to demonstrate a 20% difference between the two groups at 3 months, with 90% power and a 5% alpha risk. It was decided to include 230 patients to take into account patients who could not be evaluated.

Patient characteristics were compared by the Chi-square test or Fisher’s exact test, when necessary, for qualitative variables, and the independent Student t-test or Wilcoxon rank sum test for quantitative variables. VAS, BPI, DN4, and HAD scores were analyzed with mixed models for repeated data with an unstructured variance-covariance matrix. The time × group interaction was tested for each score. Logistic regression tested the interaction between confounding factors which could influence the incidence of pain at 3 months among the two groups.

The Woolf test was used to evaluate the interaction between the incidence of chronic pain and the study centers among the two treatment groups.

All analyses were based on the intent-to-treat principle and used R, version 2.12.0 for Windows software (R foundation for statistical computing, Vienna, Austria). The R “nlme” package was used for linear and nonlinear mixed effect models. Two-tailed P values were calculated and significance was set at 5%.

**Results**

Two hundred sixty women aged 18–85 yr with an American Society of Anesthesiologists physical status of I, II, or III, admitted for breast surgery were enrolled between September 2006 and July 2007. Finally, 236 patients were treated (fig. 1).

Final assessments had to be completed by July 2008, when all patients had a follow-up of at least 12 months (fig. 1). The two groups were not statistically different for demographic data (table 1), type of surgery, or preoperative VAS.

Measurement of pain on the VAS showed lower scores at rest and during mobilization in the first 90 min after the end of surgery in the ropivacaine group than in the control group ($P < 0.001$) (figs 2, A and B). Ropivacaine wound infiltration decreased immediate postoperative pain in the PACU and increased the percentage of pain-free patients (VAS = 0) for the first 48 h. A higher percentage of pain-free patients was observed in the ropivacaine group than in the placebo group during the first postoperative 48 h at rest and during
Table 1. Demographic Data and Characteristics of the 236 Patients Treated for the Study

<table>
<thead>
<tr>
<th></th>
<th>Ropivacaine Group</th>
<th>Saline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 117</td>
<td>n = 119</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>56 (12)</td>
<td>57 (13)</td>
</tr>
<tr>
<td>Range</td>
<td>47–65</td>
<td>48–68</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>67 (13)</td>
<td>67 (12)</td>
</tr>
<tr>
<td>Range</td>
<td>40–105</td>
<td>45–109</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td></td>
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<tr>
<td>Mean (SD)</td>
<td>25 (6)</td>
<td>25 (4)</td>
</tr>
<tr>
<td>Range</td>
<td>16.9–45.5</td>
<td>17.7–37.2</td>
</tr>
<tr>
<td>Visual analog scale (VAS) before surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.33 (0.77)</td>
<td>0.32 (0.93)</td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Range</td>
<td>0–5</td>
<td>0–7</td>
</tr>
<tr>
<td>ASA physical status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>66 (56.4)</td>
<td>62 (52.1)</td>
</tr>
<tr>
<td>II</td>
<td>48 (41.0)</td>
<td>55 (46.2)</td>
</tr>
<tr>
<td>III</td>
<td>3 (2.6)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast-conserving surgery with ALND</td>
<td>53 (45.3)</td>
<td>62 (52.1)</td>
</tr>
<tr>
<td>Mastectomy with ALND or SLND</td>
<td>53 (45.3)</td>
<td>48 (40.3)</td>
</tr>
<tr>
<td>Mastectomy without ALND or SLND</td>
<td>11 (9.4)</td>
<td>9 (7.6)</td>
</tr>
<tr>
<td>Sufentanil during surgery (µg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.34 (0.11)</td>
<td>0.33 (0.11)</td>
</tr>
<tr>
<td>Range</td>
<td>0.17–0.83</td>
<td>0.07–0.83</td>
</tr>
</tbody>
</table>

ALND = axillary lymph node dissection; ASA = American Society of Anesthesiologists; BMI = body mass index; SLND = sentinel lymph node dissection.
Ropivacaine Wound Infiltration and Chronic Pain

and 2.96 mg (0–18) for the first 48 postoperative hours in the ropivacaine and placebo groups, respectively. Following the protocol, the amount of paracetamol and ketoprofen consumed during the postoperative period was not different between the two groups. The incidence of nausea and vomiting (Apfel score > 2) was 4% in the ropivacaine and 6% in the control group ($P < 0.001$). In addition to wound infiltration, patients in the two treatment groups received the same quantities of intravenous analgesics. The time × group interaction was tested. $P$ value is associated with the test of group × time effect. VAS = visual analog scale.

No statistically significant difference was observed between the two groups in relation to potential confounding factors, such as adjuvant therapy (chemotherapy or radiotherapy), age, body mass index, type of surgery, or anxiety and depression scores (table 3).

Pain severity and pain interference on the BPI were not statistically different between groups but increased significantly in both groups over time ($P < 0.0001$ and $0.001$, respectively) (fig. 3). The maximum percentage of missing data for each point (0, 3, 6, and 12 months) in both arms was less than 5% (range: 0–5%).

A statistically significant increase was observed in the mean BPI scores (severity and interference) compared to baseline during the study in both groups ($P < 0.0001$ and $P < 0.001$, respectively) (fig. 3).

The mean DN4 scores also increased over time ($P < 0.001$) and this increase was not statistically different between the two groups ($P = 0.058$) (fig. 4).

A statistically significant improvement was observed in the anxiety score during the study ($P < 0.0001$) in both groups, whereas depression scores remained stable compared to baseline in both groups (fig. 5).

No adverse effects were observed during or just after ropivacaine wound infiltration.

No statistically significant interaction was observed between the incidence of chronic pain and study centers in the two treatment groups (Woolf test).

**Discussion**

This multicenter, prospective, randomized, double-blind, placebo-controlled study shows that ropivacaine wound infiltration after breast surgery

1. decreased immediate postoperative pain for the first 90 min in the PACU,
2. increased the percentage of pain-free patients for the first 48 h postoperatively,
3. did not decrease chronic pain at 3 months (primary objective of the study), 6 and 12 months postoperatively, and
4. did not decrease neuropathic pain at 3, 6, and 12 months postoperatively ($P = 0.058$).

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**Table 2.** Chronic Pain: Primary Outcome 3 Months after Surgery. Intention to Treat Analysis

<table>
<thead>
<tr>
<th>Primary Pain Outcome: BPI at 3 Months</th>
<th>Ropivacaine Group</th>
<th>Saline Group</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score ≥ 3: n (%)</td>
<td>37/111 (33.3%)</td>
<td>29/108 (26.9%)</td>
<td>0.37</td>
</tr>
<tr>
<td>CI 95% (Score ≥ 3, %)</td>
<td>24.5–42</td>
<td>18.4–35.2</td>
<td></td>
</tr>
<tr>
<td>Mean score (SD)</td>
<td>1.97 (2.3)</td>
<td>1.7 (2.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Range</td>
<td>0–9</td>
<td>0–9</td>
<td></td>
</tr>
</tbody>
</table>

BPI = brief pain inventory; n = number of patients; % = percentage of patients.
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No difference in anxiety and depression (HAD scores) was observed between the two groups, but anxiety decreased significantly with time.

Multivariate analysis failed to identify any risk factors for chronic pain in this study. The various types of surgery included breast tumor resection with axillary lymph node dissection, mastectomy with or without axillary lymph node dissection, and mastectomy with sentinel lymph node dissection.

In this study, the overall incidence of chronic pain at 3 months on the BPI (27 and 33% in the ropivacaine and placebo groups, respectively) was low compared to certain other published studies (20–65%), and the estimated prevalence of sensory disturbances ranges between 20 and 80%. This wide range of prevalence of pain reported in the literature is probably because of differences in the definitions of persistent pain, the frequency and period of monitoring, the methods used to measure pain, types of surgery, adjuvant therapy, number of patients studied, time to surgery, and finally the type of analgesia. However, the incidence of neuropathic pain on the DN4 (24 and 30% in the ropivacaine and placebo groups, respectively) in our patients was in the middle range compared to that reported in other studies (17–50%).

The intensity of acute postoperative pain was always less than 25 mm on the VAS, both at rest and during mobilization, which is similar to the results reported in the literature. A statistically significant difference between the two groups was only observed for the first 90 min, which is also in line with the literature and shows that local anesthetic infiltration is a potent adjuvant as part of the multimodal management of pain after breast surgery. Patients received optimal postoperative treatment with nonsteroidal anti-inflammatory drug, acetaminophen and rescue morphine (Patient-controlled Analgesia). Morphine consumption was also very low for the first 48 h in both groups (2.9 mg/48 h). Because the management of acute postoperative pain was optimal in the two groups, ropivacaine infiltration could not decrease the pain score further after the first 90 min and the pharmacokinetics of ropivacaine do not allow a sustained effect for more than 90 min.

No statistically significant difference in the incidence of chronic pain was observed on the BPI 3, 6, and 12 months after surgery. The incidence of chronic pain was low in this study, the overall incidence of chronic pain at 3 months on the BPI (27 and 33% in the ropivacaine and placebo groups, respectively) was low compared to certain other published studies (20–65%), and the estimated prevalence of sensory disturbances ranges between 20 and 80%. This wide range of prevalence of pain reported in the literature is probably because of differences in the definitions of persistent pain, the frequency and period of monitoring, the methods used to measure pain, types of surgery, adjuvant therapy, number of patients studied, time to surgery, and finally the type of analgesia. However, the incidence of neuropathic pain on the DN4 (24 and 30% in the ropivacaine and placebo groups, respectively) in our patients was in the middle range compared to that reported in other studies (17–50%).

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### Table 3. Potential Confounding Factors which May Interact with the Incidence of Chronic Pain at 3 Months among the Two Groups

<table>
<thead>
<tr>
<th>Factors</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast-conserving surgery with ALND</td>
<td>0.24</td>
</tr>
<tr>
<td>Mastectomy without ALND or SLND</td>
<td>0.42</td>
</tr>
<tr>
<td>Mastectomy with ALND or SLND</td>
<td>0.77</td>
</tr>
<tr>
<td>Age</td>
<td>0.54</td>
</tr>
<tr>
<td>BMI</td>
<td>0.93</td>
</tr>
<tr>
<td>Axillary lymphedema: yes/no</td>
<td>0.87</td>
</tr>
<tr>
<td>Radiation therapy: yes/no</td>
<td>0.62</td>
</tr>
<tr>
<td>Chemotherapy: yes/no</td>
<td>0.94</td>
</tr>
<tr>
<td>Hormonal treatment: yes/no</td>
<td>0.99</td>
</tr>
<tr>
<td>Postoperative nausea and vomiting score &gt; 2</td>
<td>0.37</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>0.98</td>
</tr>
<tr>
<td>HAD score at 3 mo</td>
<td>0.62</td>
</tr>
<tr>
<td>Anxiety score at 3 mo</td>
<td>0.45</td>
</tr>
<tr>
<td>Anxiety score ≥ 11 at 3 mo</td>
<td>0.92</td>
</tr>
<tr>
<td>Depression score at 3 mo</td>
<td>0.80</td>
</tr>
<tr>
<td>Depression score ≥ 11 at 3 mo</td>
<td>0.33</td>
</tr>
</tbody>
</table>

* P value for logistic regression to test the interaction between confounding factors which may influence the incidence of pain at 3 months, and the two treatment groups. No significant difference was observed between the two groups.

ALND = axillary lymph node dissection; BMI = body mass index; HAD = hospital anxiety and depression; SLND = sentinel lymph node dissection.

![Fig. 3. BPI scores before surgery and 3, 6, and 12 months after surgery. Pain severity and pain interference (BPI scores) increased significantly over time in both groups (P < 0.001 and P < 0.001, respectively). The increase in pain severity was statistically significant from the preoperative period until the third month, and then from the third to sixth months, while the increase in pain severity from the sixth to twelfth months was not statistically significant. The increase in pain interference was statistically significant from the preoperative period until the third month only. The time × group interaction was tested. P value is associated with the test of group × time effect. BPI = brief pain inventory.](image-url)
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Ropivacaine Wound Infiltration and Chronic Pain

study compared to the literature.6,8,32 If severe acute postoperative pain is associated with a higher incidence of chronic pain,33,34 the low incidence of chronic and neuropathic pain observed in our study could, therefore, be due to the effective control of acute postoperative pain in the two groups (30% of all patients were pain-free at rest for the first 48 h). Postoperative morphine consumption was also low, associated with a low incidence of nausea and vomiting, with no significant differences between the two groups.

Neuropathic pain was also globally identical in the two groups. Based on the results of previous studies,3 chronic pain after breast cancer surgery and adjuvant therapy is predominantly characterized by neuropathic pain, partially related to intraoperative nerve injury. Nerve-sparing techniques may reduce the incidence of neuropathic pain without totally eliminating this complication.3 Various types of pain may also coexist after breast surgery.35 In a review of neuropathic pain after breast surgery, Jung proposed four distinct pain syndromes: phantom breast pain, intercostobrachial neuralgia, neuroma pain, and other nerve injury pain.33

One hypothesis is that local or loco-regional analgesia decreased the incidence of neuropathic pain. For instance, postthoracotomy pain correspond to neuropathic characteristics.36,37 Epidural analgesia with local anesthetics decreases chronic pain 3, 6, or 12 months after thoracotomy.38

After posterior spinal arthrodesis, local anesthetic infusion at the iliac crest bone graft donor site decreased donor site pain and increased patient satisfaction at a minimum of 4 yr after surgery. In addition, none of the patients in the treatment group developed chronic iliac crest dysesthesia (0 vs. 70% in each group, respectively).39

Better control of acute postoperative pain, the antiprostaglandinflammatory properties of local anesthetics, and interruption of the nociceptive signal are the most frequent explanations proposed for this phenomenon.

Recent data show that chronic pain and other surgical, psychosocial, and socio-environmental factors are major comorbid and confounding factors.29,40–42 These results are in accordance with our results; in the current study, high anxiety scores were more frequent (70 vs. 37%) in patients with chronic pain than in the other patients. However, we did not detect any differences for the HAD scores between the two groups, which is concordant with the absence of difference in terms of chronic pain.

Similarly, 3 months after breast surgery, Fassoulaki failed to demonstrate a difference in the incidence of chronic pain with gabapentin or mexiletine, but the incidence of burning pain was statistically lower in the two active treatments groups compared to the placebo group.31

A few published studies have evaluated the prevention of chronic pain after breast surgery. Fassoulaki25 randomized 50 patients who underwent breast cancer surgery to one of two groups. Patients in the multimodal treatment group received gabapentin, topical local anesthetic and intraoperative irrigation of the brachial plexus and several intercostal

Fig. 4. DN4 scores before surgery and 3, 6, and 12 months after surgery. The mean DN4 scores increased over time (P < 0.001) and this increase was not statistically different between the two groups (P = 0.058). Only a trend for decreasing was observed in the ropivacaine group compared to control group between the sixth and the twelfth postoperative month. The time × group interaction was tested. P value is associated with the test of group × time effect. DN = neuropathic pain.

Fig. 5. HAD scores before surgery and 3, 6, and 12 months after surgery over time, anxiety scores decreased (P < 0.001) but depression scores remained stable over time. The time × group interaction was tested. P value is associated with the test of group × time effect. HAD = hospital anxiety and depression.
spaces with ropivacaine, while the control group received a placebo instead of the three active agents. Patients in the multimodal treatment group had a lower incidence of axilla pain (14 vs. 45%), arm pain (23 vs. 59%), and analgesic use (0 vs. 23%) 3 months, but not 6 months after surgery. Although previous studies have failed to demonstrate the analgesic effects of wound infiltration with local anesthetic solutions after abdominal surgery, this treatment seems to be more effective when used during minor surgery, such as inguinal hernia repair or breast surgery.25

Two other studies compared a control group with multimodal analgesia or with multimodal analgesia plus paravertebral block.18,19 Postoperative pain intensity and chronic pain at 3, 6, and 12 months were statistically lower in the paravertebral block group.18,19 In addition to providing acute postoperative pain relief, loco-regional analgesia reduces the incidence and intensity of chronic pain.

Our study has limitations. The chronic pain and neuropathic pain increased significantly over time in both groups (fig. 4). Several confounding factors were probably present in the first year after surgery delaying the resolution of persistent postoperative pain and increasing neuropathic pain: adjuvant chemotherapy and radiotherapy, anxiety, living with a diagnosis of cancer, and posttraumatic stress disorder.

No statistically significant difference in the incidence of neuropathic pain on the basis of DN4 scores was observed after surgery. To test for a statistically significant difference between the two groups, an alpha risk less than 5% was accepted (type I error: inappropriately rejecting a true null hypothesis). After testing the difference between the DN4 scores of the two groups (fig. 4), the P value was 0.058 which although close to 0.05, it still is not sufficient to consider the difference to be statistically significant. It is possible that the number of patients was not sufficient (type II error). In fact, the number of patients for this study was calculated for the main outcome (BPI scores at 3 months) and does allow a robust conclusion concerning this outcome. We did not conduct a post hoc power analysis for DN4 score comparison, but interestingly the incidence of chronic and neuropathic pain is similar as well in the published literature as in our study. The number of patients may, therefore, be sufficient for comparison of neuropathic pain allowing valid conclusions concerning this endpoint.

The absence of a statistically significant reduction in the severity and incidence of chronic pain despite the better control of acute pain in the current study could have been due to the short duration or to an insufficient analgesic potency of the local anesthetic compared to the potent prolonged multimodal analgesia given to both groups. Analgesia is probably obtained with paracetamol and ketoprofen in most patients making the combination with wound infiltration less effective. As a result other authors have used continuous wound infiltration after mastectomy to prolong analgesia.13,44 Also, thoracic paravertebral block provides better pain control than infiltration after breast surgery and comparisons of these techniques may be an area of future research in chronic pain and also in cancer free-recurrence survival.20,45,46

Conclusion
Ropivacaine wound infiltration after breast surgery increases the incidence of pain-free patients by one half in the first 48 h after surgery and decreases the pain scores in the PACU. Although the incidence of chronic pain was lower than that reported in the literature, wound infiltration does not decrease the incidence of chronic pain in the two groups.

References
16. Wickessell RK, Olsson GL: Predicting and preventing chronic postsurgical pain and disability. ANESTHESIOLOGY 2010; 113:1260–1
plasma concentration of stable nitric oxide products after breast surgery. Anesth Analg 2006; 103:995–1000