

Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery

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Editor's key points

- Regular aspirin, a form of non-steroidal anti-inflammatory drug (NSAID), has been associated with reduced risk of many cancers, including colorectal cancer.
- This retrospective analysis suggests that a single intraoperative NSAID is associated with improved disease-free survival (DFS) in women undergoing conservative breast cancer surgery.
- There also appears to be an association between higher preoperative neutrophil:lymphocyte ratio and worse DFS in conservative breast cancer surgery.

Background. An association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and better outcome after mastectomy and lung surgery for cancer has been recently suggested. In a retrospective analysis, we investigated the association between intraoperative NSAIDs use in conservative breast cancer surgery and breast cancer disease-free survival (DFS). Similarly, we also evaluated the association between breast cancer DFS and preoperative neutrophil:lymphocyte ratio (NLR).

Methods. A retrospective analysis of a single-centre cohort was performed in breast cancer patients ($n=720$) with uni- and multivariate analyses, using a Cox regression model.

Results. In conservative breast cancer surgery, the intraoperative use of NSAIDs (ketorolac or diclofenac) was associated with an improved DFS (hazard ratio (HR)=0.57 [95% confidence interval (CI): 0.37–0.89], $P=0.01$) and an improved overall survival (OS) [HR=0.35 (95% CI: 0.17–0.70), $P=0.03$]. In these patients, an NLR >3.3 (identified by a receiver-operating characteristic curve) was associated with a shorter DFS [HR=1.99 (95% CI: 1.16–3.41), $P=0.01$] and OS [HR=2.35 (95% CI: 1.02–5.43), $P=0.046$].

Conclusions. Intraoperative NSAIDs and higher preoperative NLR are associated with improved outcome in conservative breast cancer surgery. Prospective, randomized trials to evaluate if these associations are causal are warranted.

Keywords: conservative breast cancer surgery; neutrophil:lymphocyte ratio; non-steroidal anti-inflammatory drugs

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Surgery is an important component of the treatment of solid tumours. However, surgery induces an acute inflammatory response that may exacerbate some mechanisms linked to tumour growth and dissemination.¹ These mechanisms are not completely understood but could be influenced either by the tumour characteristics (e.g. size) or by the surgical technique (i.e. degree of tissue injury).¹

Retrospective analyses suggest that intraoperative use of non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with a better outcome after mastectomy and lung cancer surgery.^{2–3} Chronic administration of low-dose aspirin has been linked to improved prevention of cancer.^{4–8} However, the benefit of a single low dose of NSAID remains controversial.⁹ Consequently, some patients receive NSAIDs during conservative cancer surgery, while others do

not, regardless of their cancer staging.^{2–10} Considering that in animal models, a short course of NSAIDs appears to improve cancer survival,¹¹ it is relevant to evaluate this observation in patients undergoing less invasive (i.e. conservative) surgery.

Certain markers of inflammation have been shown to be linked to tumour progression. One of these, the neutrophil:lymphocyte ratio (NLR), which is associated with low-grade systemic inflammation, was initially linked with cardiac mortality,¹² and has since then been proposed as a prognostic factor for various types of cancer surgery.^{13–21}

In this retrospective analysis, we investigated the effect of a single intraoperative dose of ketorolac or diclofenac, and the preoperative NLR, during conservative primary breast cancer surgery, on disease-free survival (DFS).

Methods

Patients and methods

Ethical approval for this study (Ethical Committee N/REF 2010/15MAR/085, No. B40320108384) was provided by the IRB (CEBH of the Université catholique de Louvain, Brussels, Belgium. Chairperson Pr J.M. Maloteaux) on March 29, 2010. We retrospectively reviewed the existing databases of breast cancer patients undergoing breast cancer surgery.

Patients were treated and data collected according to the most recent guidelines.²²⁻²⁷ For data collection, we used the same methodology as previously described.² One thousand seven hundred and two patients were screened (Fig. 1). Seven hundred and twenty-six patients met the following inclusion criteria: tumorectomy, with or without axillary clearance between February 2003 and December 2008. Exclusion criteria were: cancer in the past 5 yr (excluding cutaneous basocellular and *in situ* uterine cervix carcinomas), previous ipsilateral, and/or non-curative surgery. Six additional patients were excluded because of incomplete medical charts. Four hundred and fifty-one patients had a preoperative leucocyte count assessed in our clinical laboratory in the 6 weeks preceding surgery and were included in the analysis. Indications for surgery were defined according to international recommendations and guidelines.²²⁻²³ These indications were discussed weekly by the multidisciplinary board of our breast clinic and regularly updated and adjusted with new international recommendations and data of the literature. All surgeries were performed by the same surgeon (M.B.) and followed-up jointly with an oncologist (J.-P.M.). Chemotherapy, radiotherapy, and hormone therapy were performed according to the international expert consensus (9th and 10th St-Gallen consensus).²²⁻²⁴⁻²⁷ After surgery, patients were followed-up trimonthly for 2 yr, then twice a year for 3 yr, and annually

thereafter. The following data were obtained from the medical records: preoperative (patient characteristic) characteristics, tumour size, histological grade and type, oestrogen and progesterone receptor status, HER-2 expression, extent of axillary nodal disease, administration of adjuvant chemotherapy, radiotherapy, or endocrine therapy. The Nottingham prognostic index was calculated based on the histological findings.²² These data were compared between patients receiving or not intraoperative NSAIDs (Table 1). Except for age, all patient and tumour characteristics were similar between the two groups.

Leucocyte count

Leucocyte count was typically included in the routine preoperative evaluation and prospectively registered in a computed database. The latest preoperative value was recorded. All venous blood samples were processed in a blood analyzer (Sysmex; TOA Medical Electronics, Kobe, Japan) for the determination of the complete blood cell counts and differential counts of leucocytes. We recorded the neutrophil and the lymphocyte counts, and calculated the NLR.

Table 1 Characteristics of 720 patients undergoing conservative breast cancer surgery after the intraoperative use of the NSAIDs ketorolac or diclofenac. Data are presented as mean (SD) (range) or as number (%). * $P=0.007$ compared with no NSAID (Student's *t*-test). NLR, preoperative neutrophil:lymphocyte ratio. Before 2009, histological grade was not determined for invasive lobular carcinoma. Lymph node invasion was analysed only if excised

	NSAIDs use (n=510)	No NSAID use (n=210)
Age (yr) (range)	56 (25-88)	60 (27-89)*
Tumour size (mm)	16 (12)	17 (9)
Histological grade		
1	99 (19%)	43 (20%)
2	182 (36%)	67 (32%)
3	179 (35%)	76 (36%)
Undetermined	50 (10%)	24 (11%)
Lymph node invasion		
None	287 (66%)	140 (76%)
1-3 positive lymph nodes	121 (28%)	35 (19%)
>3 positive lymph nodes	28 (6%)	10 (5%)
Nottingham prognostic index	6.8 (4.1)	6.8 (2.5)
Hormonal receptor status		
Oestrogen positive	434 (85%)	167 (80%)
Progesterone positive	411 (81%)	162 (77%)
HER-2 expression	50 (10%)	17 (8%)
NLR	2.71 (1.56)	2.98 (1.79)
Ketorolac use	363 (71%)	—
Diclofenac use	147 (29%)	—

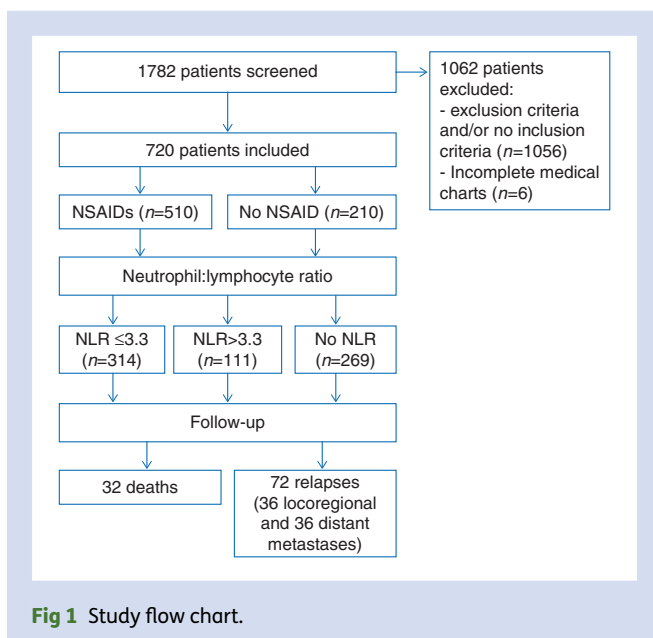


Fig 1 Study flow chart.

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