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Original article

# Therapeutic escalation – De-escalation: Data from 15.508 early breast cancer treated with upfront surgery and sentinel lymph node biopsy (SLNB)

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ABSTRACT

*Introduction:* The aim of this study was to examine changes in therapeutic practices for early breast cancer T0-2 N0 managed by upfront surgery and SLNB.
*Population:* Between 1999 and 2012, *15.508* patients were treated. Four periods were determined: 1999–2003, 2004–2006, 2007–2009 and > 2009. Five tumor subtypes were defined according to hormonal receptors (HR) and Her2: Luminal A (HR + Her2- Grade 1–2), Her2 (Her2+ HR-), Triple-negative (HR-Her2-), Luminal B Her2- (HR + Her2- Grade 3), Luminal B Her2+ (HR + HER2+).
*Methods:* Rates of axillary lymph node dissection (ALND), adjuvant chemotherapy ± trastuzumab, endocrine treatment, mastectomy and post mastectomy radiotherapy (PMRT) were analyzed according to treatment periods with univariate and multivariate analysis. Overall and disease-free survivals were analyzed according to treatment periods adjusted for HR and then for tumor subtypes.
*Results:* Rates of ALND, adjuvant chemotherapy and endocrine treatment varied significantly according to treatment periods, for HR positive and negative tumors. ALND rate decreased for all tumor subtypes with a decrease of adjuvant chemotherapy rate for Luminal A tumors and an increase for Luminal B Her2+ and Her2-tumors. Endocrine treatment rate decreased for Luminal A and increased for Luminal B Her2+ tumors. In multivariate analysis, these modifications with time remained significant. Mastectomy

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and PMRT rates increased. In multivariate analysis, overall and disease-free survivals increased during successive periods.
*Conclusion:* A global therapeutic de-escalation in ALND and adjuvant systemic treatment, combined with an actual escalation in some specific subsets was demonstrated, but without negative impact on survival.


## 1. Introduction

During the last 20 years, incidence of breast cancer worldwide and in France has risen with parallel increase in diagnosis of early tumors and decrease in mortality [1,2]. During the same period, various proposals for therapeutic de-escalation have been validated or are under evaluation, including a decrease in the indication or in the intensity of surgical and medical adjuvant treatments. Thus, conservative treatment rate, in relation with early diagnosis, oncoplastic surgery and neo adjuvant treatments gradually increased [3] with also a decrease of axillary lymph node dissection (ALND) rate since the development and validation of sentinel lymph node biopsy (SLNB) procedure for non-involved sentinel nodes (SN) [4]. More recently, since results of ACOSOG Z0011 [5,6] and IBCSG 23-01 [7] trials, complementary ALND was questioned in some situations for involved SN [8].

In a concomitant way, it was proposed to consider a decrease in adjuvant medical treatments, including radiotherapy (hypofractionnated or partial breast radiotherapy) and adjuvant chemotherapy, mostly due to the characterization of breast cancer biological subtypes with distinct outcomes and/or recent availability of multigenic signatures allowing to predict a favorable prognosis following adjuvant endocrine treatment, thereby sparing the need for cytotoxic chemotherapy in a growing number of patients [9–13]. However, the simultaneous implementations of these de-escalation strategies and their actual consequences on outcome in "real-life" have been poorly described.

The aim of this study was to examine changes in therapeutic practices and possible consequences on outcome for a large national multicenter retrospective cohort of T0-2 N0 early breast cancer managed by upfront surgery and SLNB over a period of 14 years.

## 2. Material and methods

### 2.1. Population

Between 1999 and 2012, *15.508* patients were treated by upfront surgery with SLNB for early breast cancer T0-2 N0 in 17 breast cancer units in France.

Four periods were determined: 1999–2003 (P1), 2004–2006 (P2), 2007–2009 (P3) and >2009 (P4), based on the following landmarks:

- 2003: results of the first randomized clinical trial [14], evaluating SLNB with omission of ALND for negative SN.
- 2005–2006: large implementation of adjuvant trastuzumab in HER2+ early breast cancer
- 2009: first results of NSABP B-32 and ACOSOG Z0011.

### 2.2. Criteria

Five tumor subtypes were defined according to hormonal receptors status (HR: ER and/or PR expression, with a 10% threshold of positivity) and Her2 status (determined according to French guidelines [15,16] by immunohistochemistry ± fluorescent in situ hybridization): Luminal A (HR + Her2- Grade 1–2), Her2 (Her2+ HR-), Triple negative (HR- Her2-), Luminal B Her2- (HR + Her2- Grade 3), Luminal B Her2+ (HR + Her2+). When Ki 67 is not available, SBR grade can be used to classify tumor into intrinsic subtype's classification as suggested by the St Gallen 2011 consensus [17].

Four categories of lymph node (LN) status were defined: negative LN (pN0i-), isolated tumor cells (pN0 (i+): ≤0.2 mm), detected either by hematoxylin and eosin (HE) staining or by cytokeratin immunohistochemistry (IHC), micrometastases (pN1mi: >0.2 mm and ≤2 mm), and macrometastases (>2 mm). SLNB procedure was performed using combined isotopic and colorimetric detection or isotopic detection alone with peri tumoral and or sub areolar injection. Although the methods used for SN histological examination were not standardized in the protocol, all sites proceeded similarly [18]: serial sections were performed every 200 μm and stained with standard HE. The number of sections was six to ten, or pursued until node exhaustion in case of large SN. Additional IHC analysis was done in case of negative results at standard examination. For LN identified by complementary ALND, routine HE analysis was performed.

### 2.3. Evaluation

Rates of ALND, adjuvant chemotherapy ± trastuzumab, endocrine treatment for HR + tumors, mastectomy and post mastectomy radiotherapy, regional nodal irradiation (RNI) were analyzed according to treatment periods with univariate and multivariate analysis.

Overall (OS) and disease-free (DFS) survivals were analyzed according to treatment periods adjusted for HR and then for tumor subtypes.

### 2.4. Statistics

We used standard descriptive statistics (mean, standard deviation [SD], median and range for quantitative variables, count and frequency for categorical variables) to describe patients and tumors characteristics. In univariate analyses, comparisons of proportions were performed using Chi-Square test. In order to determine factors independently correlated to treatment methods, multivariate analysis was performed using binear logistic regression. DFS was defined as the time from surgery to breast, node, distant relapse or death. OS was defined as the time from surgery to death. Survival analyses were performed using Log-rank test for univariate analysis and Cox model for multivariate analysis.

All statistical tests were two-sided. The level of statistical significance was set at a p value of 0.05. Statistical analyses were performed with the SPSS version 16.0.

## 3. Results

### 3.1. Population according to successive periods

Characteristics of patients according to periods are reported in