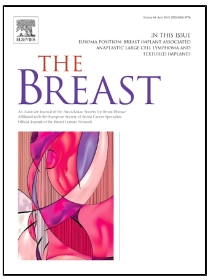
# Trends in axillary lymph node dissection for early-stage breast cancer in Europe : impact of evidence on practice

# Accepted Manuscript

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|---|---|
| PII: | S0960-9776(19)30041-4 |
| DOI: | 10.1016/j.breast.2019.03.002 |
| Reference: | YBRST 2874 |
| To appear in: | *The Breast* |
| Received Date: | 01 January 2019 |
| Accepted Date: | 07 March 2019 |

Please cite this article as: Carlos A. Garcia-Etienne, Robert E. Mansel, Mariano Tomatis, Joerg Heil, Laura Biganzoli, Alberta Ferrari, Lorenza Marotti, Adele Sgarella, Antonio Ponti, Mahmoud Danaei, Elmar Stickeler, Dimitri Sarlos, Annemie Prové, Olivia Pagani, Gilles Berclaz, Klinik Engeried, Mario Taffurelli, Elisabetta Cretella, Didier Verhoeven, Andreas Denk, Birgit Carly, Bettina Ballardini, Yvonne van Riet, Rainer Kimmig, Mattea Reinisch, Catia Angiolini, Volker Möbus, Gunter Emons, Kay Friedrichs, Andreas Schneeweiss, Corrado Tinterri, Daniel Egle, Gracienne Staelens, Marion Kiechle, Nadia Harbeck, Fabio Corsi, Lorenzo Menghini, Augusto Lombardi, Lucio Fortunato, Marina Bortul, Jens Huober, Farzaneh Badbanchi, Christoph Tausch, Trends in axillary lymph node dissection for early-stage breast cancer in Europe: impact of evidence on practice, *The Breast* (2019), doi: 10.1016/j.breast.2019.03.002

# Trends in axillary lymph node dissection for early-stage breast cancer in Europe: impact of evidence on practice

Carlos A. Garcia-Etienne, M.D.[1,^], Robert E. Mansel, M.D.[2], Mariano Tomatis, B.Sc.[3], Joerg Heil, M.D.[4], Laura Biganzoli, M.D.[5, 6], Alberta Ferrari, M.D.[1], Lorenza Marotti, PhD[6], Adele Sgarella, M.D.[1], Antonio Ponti, M.D.[3] and the EUSOMA Working Group*

1 Breast Surgery, Fondazione IRCCS Policlinico San Matteo, Università degli Studi di Pavia, Italy
2 School of Medicine, Cardiff University, United Kingdom
3 AOU Città della Salute e della Scienza, CPO Piemonte and EUSOMA Data Centre, Turin, Italy
4 University of Heidelberg, Germany
5 Nuovo Ospedale di Prato, Italy
6 EUSOMA, Florence, Italy

^ Corresponding Author (requests for reprints):
Carlos A. Garcia-Etienne, M.D.
Breast Surgery, Fondazione IRCCS Policlinico San Matteo, *Università degli Studi di Pavia*
Viale Camillo Golgi 19.
Pavia, 27100
Italy
Work phone: +39 0382 501809
Fax: +39 0382 503101
email: carlos.garciaetienne@unipv.it

**Category:** Original article.

**Running Head:** Trends in axillary dissection for breast cancer in Europe

**Keywords:** axillary lymph node dissection; axillary dissection; axillary surgery; axillary lymphadenectomy; positive sentinel node; Z0011; surgery for breast cancer.

*Members of the EUSOMA Working Group:
Mahmoud Danaei, Brustcentrum Aachen Marienhospital, Aachen, Germany;
Elmar Stickeler, University Medical Center and Luisenhospital, Aachen Germany;
Dimitri Sarlos, Brustzentrum Mittelland Kantonsspitaeler Aarau/Olten, Switzerland;
Annemie Prové, Breast Center Sint Augustinus, Wilrijk, Antwerpen, Belgium;
Olivia Pagani, Centro di Senologia della Svizzera Italiana, Ospedali Regionali di Lugano, Bellinzona e Valli, Switzerland;
Gilles Berclaz, Breast Centre Bern, Division of Gynaecology & Surgical Oncology, Klinik Engeried, Lindenhofgruppe, Bern, Switzerland;
Mario Taffurelli, Breast Cancer Unit, Policlinico Sant'Orsola Malpighi, University of Bologna, Italy;
Elisabetta Cretella, GIPMa, Comprensorio Sanitario di Bolzano, Italy;
Didier Verhoeven, University of Antwerp; Breast Clinic Voorkempen, Brasschaat, Belgium;
Andreas Denk, Brustzentrum St. Joseph-Stift, Bremen, Germany;

Birgit Carly, Breast Unit and Prevention Center Isala, Department Gynecology-Obstetrics, CHU-UMC St Pierre, Brussels, Belgium;
Bettina Ballardini, Centro Senologia Multimedica, Italy;
Yvonne van Riet, Catharina Hospital, Eindhoven, The Netherlands;
Rainer Kimmig, West German Cancer Center, Breast Unit, University Hospital Essen, Germany;
Mattea Reinisch, Breast Unit, Kliniken Essen-Mitte, Germany;
Catia Angiolini, Breast Unit e Gruppo Oncologico Multidisciplinare Tumori della Mammella, DAI Oncologico e di Chirurgia ad indirizzo robotico, Azienda Ospedaliero Universitaria Careggi, Firenze, Florence, Italy;
Volker Möbus, Breast Unit, Klinikum Frankfurt Höchst, Academic Hospital, Frankfurt, Germany;
Gunter Emons, Department of Obstetrics & Gynecology, University of Goettingen, Germany;
Kay Friedrichs, Mammazentrum, Hamburg, Germany;
Andreas Schneeweiss, Breast Unit University of Heidelberg, Germany;
Corrado Tinterri, Breast Unit Humanitas Cancer Center, Rozzano, Italy;
Daniel Egle, Leitender Oberarzt BGZ Tirol
Univ. Frauenklinik Innsbruck, Austria;
Gracienne Staelens, Borstkliniek Kortrijk AZ Groeninge, Belgium;
Marion Kiechle, University Hospital Klinkum Rechts der Isar, Department of Gynecology, Technical University Munich, Germany;
Nadia Harbeck, Breast Center, University of Munich LMU, Germany;
Fabio Corsi, Breast Unit, Istituti Clinici Scientifici Maugeri, Pavia, Italy;
Lorenzo Menghini, AUSL Romagna, Breast Unit Rimini, Italy;
Augusto Lombardi, Breast Surgery Unit, University of Rome La Sapienza, Sant'Andrea Hospital, Rome, Italy;
Lucio Fortunato, Centro di Senologia Azienda Ospedaliera San Giovanni Addolorata, Rome, Italy;
Marina Bortul, SSD Breast Unit - ASUITS - Azienda Sanitaria Universitaria Integrata di Trieste, Italy;
Jens Huober, Comprehensive Cancer Center Ulm, Germany;
Farzaneh Badbanchi, Breast Unit, Dr. Horst Schmidt Klinken, Wiesbaden, Germany;
Christoph Tausch, Breast Center Zurich Seefeld, Switzerland.

**ABSTRACT**

**BACKGROUND**

Data from recently published trials have provided practice-changing recommendations for the surgical approach to the axilla in breast cancer. Patients with T1-2 lesions, treated with breast conservation, who have not received neoadjuvant chemotherapy and have 1-2 positive sentinel nodes (Z0011-criteria) may avoid axillary lymph node dissection (ALND). We aim to describe the dissemination of this practice in Europe over an extended period of time.

**METHODS**

Our source of data was the eusomaDB, a central data warehouse of prospectively collected information of the European Society of Breast Cancer Specialists (EUSOMA). We identified cases fulfilling Z0011-criteria from 2005 to 2016 from 34 European breast centers and report trends in ALND. Data derived from Germany, Italy, Belgium, Switzerland, Austria, and Netherlands.

**RESULTS**

6 671 patients fulfilled Z0011-criteria. Rates of ALND showed a statistically significant decrease from 2010 (89%) to 2011 (73%), reaching 46% in 2016 ($p < 0.001$). After multivariable analysis, factors associated with higher probability of ALND were earlier year of surgery, younger age, increasing tumor size and grade, and being operated in Italy ($p < 0.001$). The minimum and maximal rates of ALND in the most recent two-year period (2015-2016) were 0% and 83% in two centers located in different countries ($p < 0.001$).

**CONCLUSION**

Our study demonstrates, a decrease in rates of ALND that started after year 2010 through the end of the study period. Wide differences were observed among centers and countries indicating the need to spread unified clinical guidelines in Europe to allow for homogeneous evidence-based practice patterns.

## INTRODUCTION

The surgical approach to the axilla in breast cancer has been a controversial issue for the last three decades.[1] Data from recently published trials have provided practice-changing recommendations for the indications of axillary lymph node dissection (ALND).

The most cited and discussed recent study is the Z0011 trial, a randomized controlled trial (RCT) from the American College of Surgeons Oncology Group (ACOSOG) that included patients with T1-2 (≤5 cm) N0 disease who were candidates for breast conservation with whole breast radiotherapy (BCT), had not received neoadjuvant chemotherapy, and had 1 to 2 positive sentinel nodes (micro or macrometastasis).[2,3] Four hundred forty-six cases were randomized to no further surgical treatment of the axilla (sentinel lymph node biopsy [SLNB]-only) and 445 cases to completion ALND. Their most recent update with a median follow-up of 9.25 years confirmed a 10-year cumulative incidence of locoregional recurrence similar for both groups (5.3% SLNB-only vs. 6.2% ALND group [p = 0.36]) and a 10-year overall survival (OS) of 86.3% in the SLND-only group and 83.6% in the ALND group (p = 0.02). [4,5]

From 2011 to 2012, the National Comprehensive Cancer Network (NCCN) guideline in the USA was modified to consider no further axillary surgery in cases who meet all Z0011 selection criteria (T1-2 lesions, 1-2 positive SLNs, candidates for BCT, no neoadjuvant chemotherapy).[6] The American Society of Clinical Oncology (ASCO) has also stated in its update of recommendations that clinicians should not recommend ALND for the same group of patients.[7] Changes in recommendations have generated controversy in some groups, arguing that omitting ALND should be based on individual cases and that more evidence is needed to inform practice.[8,9]

The adoption of a more conservative approach to the axilla in Europe after the publication of the Z0011 and other recent trials seems to be heterogeneous across countries. A study by Gondos et al, included a questionnaire to compare the surgical approach to the axilla during year 2014 among centers from Denmark, Norway, Sweden, Netherlands, Belgium, Italy, Germany and Hungary. The survey indicated that ALND is performed after micrometastasis-only in the SLN at the Institute Jules Bordet in Brussels while the Netherlands Cancer Institute is carrying out its own trial. The Hospital at the University of Heidelberg has adopted modified criteria from the ACOSOG Z0011 trial to avoid ALND since September 2010, while the Istituto Nazionale dei Tumori from Milan incorporated a similar approach since 2013. Z0011 criteria had not been implemented (as of 2014) in Denmark, the Institute Jules Bordet or the National Institute of Oncology in Hungary.[10]

A recent Dutch population-based study reported by Poodt and colleagues carried out a subgroup analysis that aimed to assess the impact of Z0011 and AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery?)[14] studies on axillary dissection in patients with cT1-2 N0 disease and 1 to 2 positive sentinel nodes who received BCT or mastectomy from 2011 to 2015. The analysis included 8 191 patients and showed a decrease in ALND from 75% in 2011 to 17% in 2015 ($p < 0.001$) for both groups, with a more pronounced and sustained decrease for cases receiving BCT (72% ALND in 2011 to 11% in 2015).[11] However, this study depicted a single European country.

We present time trends in ALND in patients with selection criteria from the Z0011 trial in 34 EUSOMA certified breast centers from 2005 to 2016 and assess heterogeneity among centers or countries with the aim to evaluate impact of evidence on practice.

## MATERIALS AND METHODS

### *eusomaDB: EUSOMA data warehouse*

The European Society of Breast Cancer Specialists (EUSOMA [originally European Society of Mastology]) has fostered a voluntary certification process for breast centers to establish minimum standards and ensure multidisciplinary care. Prospectively collected information on primary breast cancer cases diagnosed and treated in each unit is transferred annually to a central EUSOMA data warehouse (eusomaDB) for continuous monitoring of quality indicators. The eusomaDB Working Group consists of centers that provide data and comply with EUSOMA requirements.[12]

The database includes (as of October 2018) over 120 000 cancers from 78 breast centers located in Germany, Sweden, Switzerland, Belgium, Austria, The Netherlands, Spain, Portugal, Italy, and China. Data include de-identified patient and tumor characteristics, information about preoperative work-up, multidisciplinary management, and follow-up. Participating centers agree to use the database for certification purposes and for cooperative clinical research. Only centers contributing with at least five consecutive years of data were included and provided consent for the study.

***Patients***

The scope of this study was to analyze trends in ALND in patients with Z0011 selection criteria; therefore, we included patients with newly diagnosed unilateral early-stage breast cancer with T1-2 (≤5 cm) lesions treated with BCT, who had a positive sentinel node biopsy (micro or macroscopic disease), and had not received neoadjuvant chemotherapy.

Out of 75 168 cases registered in the database from 34 breast centers located in 6 countries (13 in Germany, 11 in Italy, 4 in Belgium, 4 in Switzerland, 1 in Austria, and 1 in the Netherlands) with a final pathology diagnosis of ductal carcinoma *in situ* (DCIS), microinvasive or invasive carcinoma, we excluded 8 903 cases with DCIS (pTis), 593 with pTX, 1 149 pT0, 3 050 pT3, 215 pT4 tumors, and 1 329 with missing information on pT;

furthermore, we excluded 5 546 cases with a preoperative clinically positive axilla or other regional metastasis (cN1-3), as well as 9 164 with SLNB not performed, and 34 914 with negative sentinel lymph node, node not found, or with unknown result; 65 patients with distant metastatic disease at diagnosis, 49 cases who did not undergo surgery, and 239 patients who received neoadjuvant chemotherapy. Additionally, cases coded with simultaneous bilateral breast cancer (n = 224) or multiple lesions within the breast (n = 170), and 47 cases with a previous history of ipsilateral breast malignancy were also excluded. Moreover, we excluded 2 825 cases operated with mastectomy and 15 cases with missing information on axillary surgery (Fig 1).

Our study population for the twelve-year (2005-2016) trend analysis consisted of a total of 6 671 patients who met Z0011 selection criteria. The database does not contain information on the number of positive sentinel lymph nodes, precluding identification of cases with more than 1 positive sentinel node.

### *Statistical Analysis*

Heterogeneity of axillary lymph node dissection rates among centers was assessed using the $x^2$ test. Correlated variables (year of surgery, age group, pT, tumor histology and grade, ER status, and country) were analyzed with a multivariable logistic model to adjust the proportion of ALNDs. A trend analysis was performed from 2005 to 2016 through the Joinpoint regression method. Statistical analyses were performed with program R (version 2.10.1).

## RESULTS

Clinicopathologic characteristics of the 6 671 T1-2 N0 M0 patients who underwent breast-conserving surgery and had a positive SLNB from 2005 to 2016 are shown in Table 1.

Mean age was 59 years old (range 21–93), with 266 (4%) patients younger than 40 years, 5 001 (75%) aged 40 to 69 years, and 1 390 (21%) patients aged ≥70 years. Mean tumor size was 1.85 cm (range 0.1-5.0 cm), with 4 362 (65.3%) being pT1 lesions. Tumor histology was invasive ductal carcinoma (IDC) in 5 857 (87.8%) cases and invasive lobular carcinoma (ILC) in 544 (8.2%). More than half of tumors (59.6%) were grade II and 6 043 (90.6%) were estrogen receptors positive.

Cases in the dataset derived from 6 countries, 2 802 (42%) from Germany, 2 455 (36.8%) from Italy, and 1 414 (21.2%) from Belgium, Switzerland, Austria, and Netherlands (grouped as "other countries" for the analysis).

Some type of adjuvant systemic treatment (chemo and/or endocrine therapy) was administered to 5 991 (89.8%) cases (8.5% unknown); chemotherapy in 3 571 (53.5%) patients (11.5% unknown); endocrine therapy in 4 960 (74.4%) (17.3% unknown). Radiotherapy was delivered to 5 878 (88%) cases (8% unknown).

Rates of ALND remained constant from 2005 (87%) to 2010 (89%) ($p = 0.38$) and dropped to 73% in 2011 ($p < 0.001$), after publication of Z0011 results. The decrease was sustained reaching 46% in 2016 (Table 2; Fig 2). The Joinpoint regression analysis indicated a significant reduction rate of 12% per year from 2010 to 2016 ($p < 0.001$).

Rates of ALND decreased steeply in Germany from 91.5% in 2010 to 64.7% in 2011, to 38.4% in 2013, down to 17% in 2016. The same figures for Italy were 91.5% in 2010, 87.4% in 2011, 73.5% in 2013, and 64.2% in 2016. Belgium, Switzerland, Austria, and Netherlands were analyzed together due to the smaller number of cases in the dataset and also showed a sharp decrease in ALND rates from 79.7% in 2010 to 69.2% in 2011, to 43.6% in 2013, to 30.3% in 2016 (Fig 3).

A multivariable model adjusted for year of surgery, age group, pT, tumor histology and grade, ER status, and country of treatment showed that factors associated with increased

probability of ALND were earlier year of surgery, younger age, increasing tumor size, increasing tumor grade, and being operated in Italy ($p < 0.001$) (Table 2).

For cases operated in the most recent two-year period (2015-2016), the minimum and maximal observed rates of axillary lymph node dissection were 0% (0/23) and 83% (34/41) ($p < 0.001$) in two centers located in different countries.

## DISCUSSION

Based on the eusomaDB, we were able to show a significant trend of decreasing rates of ALND in cases fulfilling Z0011 selection criteria. The trend started from 2010 to 2011 with a sustained decrease during the whole study period (end 2016).

Additional recently published trials question the impact of ALND in early-stage breast cancer. The 23-01 trial, from the International Breast Cancer Study Group, included patients with T1-2 lesions with a positive SLNB for micrometastasis and randomized cases to completion ALND (n=465) or no further surgical treatment (n=469). With a median follow-up of 9.7 years, 10-year DFS was 76.8% (95% CI, 72.5-81.0) in the non-ALND group compared with 74.9% (70.5-79.3) in the ALND group (HR 0.85, 95% CI, 0.65-1.11; log-rank $p = 0.24$; $p = 0.0024$ for non-inferiority).[13]

The AMAROS trial from the European Organisation for Research and Treatment of Cancer, selected patients with similar Z0011 criteria, but also included cases operated with mastectomy. Patients were randomized to completion ALND or axillary radiotherapy. After a median follow-up of 6.1 years, there were no significant differences in 5y-axillary recurrence, 5y-DFS and 5y-OS between the two groups (95% CI 0.00-5.27; $p = 0.18$; $p = 0.34$, respectively). The study did show a statistically significant difference in the 5-year incidence of measured arm lymphedema, with 13% after ALND and 5% in the radiotherapy group ($p = 0.0009$).[14]

The INT09/98 trial by Agresti and colleagues addressed whether ALND could be safely avoided and whether tumor biology could adequately guide adjuvant treatment.[15] This study was not conducted in patients with a positive sentinel lymph node, but in cases with a clinically negative axilla and pT1 tumors (mean size 1.5 cm). Cases were randomized to BCT with or without ALND with no attempt to irradiate the axilla. After a median follow-up of 127 months, no statistically significant differences were observed in 10-year DFS (92.4% ALND group vs. 91.3% non-ALND group [log-rank p = 0.97]) and 10-year OS (93.3% ALND group vs. 91.5% non-ALND group [log-rank p = 0.436]). The study showed a higher rate of axillary recurrence in the non-ALND group (9%) vs. the ALND group (0%). Patients with axillary recurrence underwent ALND and no significant relationship was observed between OS and the number of involved lymph nodes in these cases.[15]

The evidence described above has led to a change in guidelines for a more conservative approach of the axilla. A study by Yao and colleagues from the National Cancer Data Base in the USA evaluated the trend of lymph node removal from 1998 to 2011 of 74 309 patients fulfilling Z0011 selection criteria. They categorized cases with not more than 4 lymph nodes removed as having had SLNB-only (n = 17 630 patients). The proportion of patients avoiding ALND increased from 23% in 2009 to 56% in 2011 ($p < 0.001$), after the publication of Z0011 results.[16] However, a recent survey reported by Morrow that aimed to determine surgeon acceptance of Z0011 findings in the US showed that still 49% (175/357) of surgeons would recommend ALND for 1 SLN macrometastasis and 62.6% (221/353) for 2 SLNs with macrometastasis. Lower propensity for ALND was significantly associated with surgeons who treated a higher volume of cases per year (21-50 cases: −0.19; >51 cases: −0.48; $p < 0.001$), surgeons who follow the recommendation of "no-ink-on-tumor" as a negative margin (1-5 mm margin: −0.10; no-ink-on-tumor: −0.53; $p < 0.001$), and those with a higher proportion of cases discussed in a multidisciplinary tumor board (1%-9% of cases: −0.25;

>9% of cases: −0.37; p = 0.02), indicating the need for education targeted toward lower-volume breast surgeons.[17]

Few recent reports explore this scenario in Europe. The study by Gondos lacked data for the period after publication of the Z0011 and other additional studies.[10] The recent Dutch report showed a clearer picture, with a sustained decrease in ALND from 72% in 2011 to 11% in 2015 for cases fulfilling Z0011 and AMAROS criteria receiving BCT. For their whole studied population, factors associated with increased probability of performing ALND were earlier year of diagnosis, younger age, primary mastectomy, invasive lobular carcinoma, increasing tumor grade, and having surgery at a nonteaching hospital (p <0.001).[11] Our analysis concurred with this study in some factors associated with ALND such as earlier year of surgery, younger age, increasing tumor size (as a partial surrogate of primary mastectomy), and increasing tumor grade.

A recent study from Germany analyzed ALND trends in 13 741 cases that met Z0011 criteria deriving from 179 breast centers from 2008 to 2015. Completion ALND decreased from 94.6% in 2008 to 46.9% in 2015 (p < 0.001). Factors associated with ALND were fewer removed SLNs, 2 metastatic SLNs, younger age, lower case volume per year, higher tumor grade and presence of lymphovascular invasion.[18]

Some factors associated with increased likelihood of performing ALND in our study may find a partial explanation on initial concerns with the Z0011 results. Regarding age, young patients, especially under 40 years were likely to be underrepresented in the trial due to the natural history of the disease that tends to present in older women and due to a selection bias before enrollment. Although the trial accepted women starting from age 18 years, close to 65% of patients were older than 50 years.[2–5] An unplanned analysis has suggested that younger patients (defined as premenopausal) should not have different outcomes when omitting ALND.[19] However, this post hoc analysis may need further validation. Regarding

tumor size, although Z0011, 23-01 and AMAROS trials could include cases with tumors up to 5 cm, the great majority of recruited patients had small to medium size lesions. In trial 23-01, 92% of cases had tumors <3 cm.[13] In AMAROS and Z0011 trials, approximately 80% and 70% of patients had T1 lesions, respectively.[2–5,14] This distribution was likely the result of a selection bias prior to randomization.

With regard to geographical differences illustrated in this report (Figure 3), it is quite challenging to find a plausible explanation with the available data, especially for the very early period right after the publication of Z0011 results (2010-2011) where a straight day-after evidence-based adherence was noted in German centers, whereas for Italian centers the change in practice seemed somehow slower.

Many randomized trials which extensive discussion is not the scope of this article have recently emerged in Europe. On one end, the SOUND (Sentinel node vs Observation after axillary Ultra-souND; Italy) trial takes one step ahead the Z0011 and aims to determine if axillary staging could even be omitted in cases with cT1 cN0 disease.[20,21] On the other end, reluctance to fully accept evidence from the Z0011 study and/or interest in solving new questions have recently initiated the following trials for cN0 patients in European countries: POSNOC (POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy; UK), INSEMA (Intergroup Sentinel Mamma; Germany/Austria), BOOG 2013-07 (The value of completion axillary treatment in sentinel node positive breast cancer patients undergoing a mastectomy; Netherlands), SINODAR ONE (Randomized Clinical Trial to Assess the Role of Axillary Surgery in Breast Cancer Patients with One or Two Macrometastatic Sentinel Nodes; Italy), and SENOMAC (Omission of Axillary Clearance in Breast Cancer Patients with Sentinel Node Macrometastases; Sweden).[22–28] BOOG 2013-07 and SENOMAC propose to answer additional questions not addressed by the Z0011 study by selecting patients with higher

tumor burden, whereas INSEMA trial contemplates a wide design that approaches more than one clinical question with a high observational power.

It should be noted that our study only included data deriving from six European countries, hence precluding a clear illustration of a wider geographical area. Moreover, datasets divided by country do not necessarily portray the standard practice across that nation, as data derived from a limited number of centers.

The most remarkable observation from our study is that, for cases operated in the most recent two-year period (2015-2016), reported rates of ALND were as wide as 0% to 83%. This seems counterintuitive, as participating centers have been certified by EUSOMA, which maintains a data warehouse and provides annual feedback on a number of performance measures, although it should be noted that omitting ALND in this scenario has not yet been introduced as a quality indicator.[12,29] Along with EUSOMA's policy, Javid and Anderson have recently advocated to monitor adherence to quality metrics and to make surgeons aware of their own performance relative to peers.[30]

## CONCLUSION

Our study demonstrates, in this European dataset of cases fulfilling the Z0011 trial selection criteria, a statistically significant decrease in rates of axillary lymph node dissection that started after publication of the trial with a sustained reduction through the end of the study period. Factors associated with increased probability of ALND were earlier year of surgery, younger age, increasing tumor size, increasing tumor grade, and being operated in Italy. Wide differences in patient management were observed among centers and countries indicating the need to formulate and spread unified clinical guidelines and benchmarking in Europe to allow for homogeneous evidence-based practice patterns.

**Acknowledgements:**

Special acknowledgements to Dr. Wolfgang Gatzemeier (Breast Unit Humanitas Cancer Center, Rozzano, Italy), Prof. Christoph Rageth (Breast Center Zurich Seefeld, Switzerland), and Prof. Christof Sohn (Breast Unit University of Heidelberg, Germany) for contribution with data and to Tiziana Tarasco (EUSOMA, Florence, Italy) for clerical assistance.

**Conflict of interest statement:**
No conflicts declared.

**Funding/Support:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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## FIGURE LEGENDS

**Figure 1.** Study population: 6 671 T1-2 N0 M0 patients who underwent breast-conserving surgery, had not received neoadjuvant chemotherapy and had a positive sentinel node from 2005 to 2016.

**Figure 2.** Rates of axillary lymph node dissection from 2005 to 2016 in T1-2 N0 M0 sentinel node positive patients who underwent breast-conserving surgery and had not received neoadjuvant chemotherapy.

**Figure 3.** Rates of axillary lymph node dissection by country from 2005 to 2016 in T1-2 N0 M0 sentinel node positive patients who underwent breast-conserving surgery and had not received neoadjuvant chemotherapy.

**Table 1.** Clinicopathologic characteristics of 6 671 T1-2 N0 M0 sentinel node positive patients who had not received neoadjuvant chemotherapy and underwent breast-conserving surgery with proportion of performed axillary lymph node dissection.

| | | N | % | No ALND | ALND | % ALND | p-value * |
|---|---|---|---|---|---|---|---|
| | | 6671 | | 1930 | 4741 | 71% | |
| **Year of surgery** | 2005 | 234 | 3.5% | 30 | 204 | 87% | **<0.001** |
| | 2006 | 316 | 4.7% | 28 | 288 | 91% | |
| | 2007 | 396 | 5.9% | 44 | 352 | 89% | |
| | 2008 | 500 | 7.5% | 57 | 443 | 89% | |
| | 2009 | 646 | 9.7% | 65 | 581 | 90% | |
| | 2010 | 726 | 10.9% | 78 | 648 | 89% | |
| | 2011 | 806 | 12.1% | 219 | 587 | 73% | |
| | 2012 | 672 | 10.1% | 225 | 447 | 67% | |
| | 2013 | 576 | 8.6% | 250 | 326 | 57% | |
| | 2014 | 634 | 9.5% | 294 | 340 | 54% | |
| | 2015 | 612 | 9.2% | 339 | 273 | 45% | |
| | 2016 | 553 | 8.3% | 301 | 252 | 46% | |
| **Age** | Mean | 59 | | | | | |
| | Range | 21-93 | | | | | |
| **Age group** | 21-39 | 266 | 4.0% | 57 | 209 | 79% | **<0.001** |
| | 40-49 | 1350 | 20.2% | 307 | 1043 | 77% | |
| | 50-59 | 1819 | 27.3% | 503 | 1316 | 72% | |
| | 60-69 | 1832 | 27.5% | 548 | 1284 | 70% | |
| | 70-79 | 1088 | 16.3% | 374 | 714 | 66% | |
| | 80+ | 302 | 4.5% | 135 | 167 | 55% | |
| | Unknown | 14 | 0.2% | 6 | 8 | 57% | |
| **Tumor size** | Mean (cm) | 1.85 | | | | | |
| | Range (cm) | 0.1-5.0 | | | | | |
| **pT** | pT1mic/a | 108 | 1.6% | 42 | 66 | 61% | **<0.001** |
| | pT1b | 790 | 11.8% | 269 | 521 | 66% | |
| | pT1c | 3464 | 51.9% | 1019 | 2445 | 71% | |
| | pT2 | 2309 | 34.6% | 600 | 1709 | 74% | |
| **Histologic subtype** | IDC | 5857 | 87.8% | 1679 | 4178 | 71% | **0.005** |
| | ILC | 544 | 8.2% | 186 | 358 | 66% | |
| | Other | 270 | 4.0% | 65 | 205 | 76% | |
| **Grade** | I | 888 | 13.3% | 322 | 566 | 64% | **<0.001** |
| | II | 3978 | 59.6% | 1159 | 2819 | 71% | |
| | III | 1778 | 26.7% | 441 | 1337 | 75% | |
| | Unknown | 27 | 0.4% | 8 | 19 | 70% | |
| **ER** | ER+ | 6043 | 90.6% | 1791 | 4252 | 70% | **<0.001** |
| | ER- | 585 | 8.8% | 132 | 453 | 77% | |
| | Unknown | 43 | 0.6% | 7 | 36 | 84% | |
| **Country** | Germany | 2802 | 42.0% | 707 | 2095 | 75% | **<0.001** |
| | Italy | 2455 | 36.8% | 566 | 1889 | 77% | |
| | Other ** | 1414 | 21.2% | 657 | 757 | 54% | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **CT** | Yes | 3571 | 53.5% | 711 | 2860 | 80% | **<0.001** |
| | No | 2334 | 35.0% | 1003 | 1331 | 57% | |
| | Unknown | 766 | 11.5% | 216 | 550 | 72% | |
| **Endocrine therapy** | Yes | 4960 | 74.4% | 3421 | 1539 | 69% | **<0.001** |
| | No | 560 | 8.4% | 405 | 155 | 72% | |
| | Unknown | 1151 | 17.3% | 915 | 236 | 79% | |
| **RT** | Yes, breast | 2304 | 34.5% | 729 | 1575 | 68% | **<0.001** |
| | Yes, breast+axilla | 680 | 10.2% | 213 | 467 | 69% | |
| | Yes, NS | 2894 | 43.4% | 782 | 2112 | 73% | |
| | No | 254 | 3.8% | 87 | 167 | 66% | |
| | Unknown | 539 | 8.1% | 119 | 420 | 78% | |

* Univariable chi square test.
** Other countries: Belgium, Switzerland, Austria and Netherlands.
ALND = axillary lymph node dissection; pT = pathologic tumor size classification; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; ER = estrogen receptors; RT = radiotherapy; NS = not specified; CT = chemotherapy.

**Table 2.** Univariable and multivariable analyses (adjusted for year of surgery, age group, pT, tumor histology and grade, ER status, and country of treatment) for the performance of axillary lymph node dissection (ALND) in 6 671 T1-2 N0 M0 sentinel node positive patients who underwent breast-conserving surgery and had not received neoadjuvant chemotherapy.

| | | N | % ALND | Univariable | | Multivariable | |
|---|---|---|---|---|---|---|---|
| | | 6671 | 71% | OR crude | p-value | OR adj. | p-value |
| Year of surgery | 2005 | 234 | 87% | ref. | | ref. | |
| | 2006 | 316 | 91% | 1.51 | 0.137 | 1.61 | 0.092 |
| | 2007 | 396 | 89% | 1.18 | 0.520 | 1.32 | 0.284 |
| | 2008 | 500 | 89% | 1.14 | 0.579 | 1.30 | 0.284 |
| | 2009 | 646 | 90% | 1.31 | 0.245 | 1.47 | 0.110 |
| | 2010 | 726 | 89% | 1.22 | 0.383 | 1.33 | 0.228 |
| | 2011 | 806 | 73% | 0.39 | **<0.001** | 0.42 | **<0.001** |
| | 2012 | 672 | 67% | 0.29 | **<0.001** | 0.28 | **<0.001** |
| | 2013 | 576 | 57% | 0.19 | **<0.001** | 0.16 | **<0.001** |
| | 2014 | 634 | 54% | 0.17 | **<0.001** | 0.14 | **<0.001** |
| | 2015 | 612 | 45% | 0.12 | **<0.001** | 0.10 | **<0.001** |
| | 2016 | 553 | 46% | 0.12 | **<0.001** | 0.09 | **<0.001** |
| | | | | | | | |
| Age group | 21-39 | 266 | 79% | 1.40 | **0.033** | 1.09 | 0.616 |
| | 40-49 | 1350 | 77% | 1.30 | **0.002** | 1.21 | **0.041** |
| | 50-59 | 1819 | 72% | ref. | | ref. | |
| | 60-69 | 1832 | 70% | 0.90 | 0.132 | 0.81 | **0.009** |
| | 70-79 | 1088 | 66% | 0.73 | **<0.001** | 0.72 | **<0.001** |
| | 80+ | 302 | 55% | 0.47 | **<0.001** | 0.45 | **<0.001** |
| | Unknown | 14 | 57% | 0.51 | 0.214 | 1.29 | 0.669 |
| | | | | | | | |
| pT | pT1mic/a | 108 | 61% | ref. | | ref. | |
| | pT1b | 790 | 66% | 1.23 | 0.322 | 1.55 | 0.069 |
| | pT1c | 3464 | 71% | 1.53 | **0.035** | 1.97 | **0.003** |
| | pT2 | 2309 | 74% | 1.81 | **0.003** | 2.65 | **<0.001** |
| | | | | | | | |
| Histologic subtype | IDC | 5857 | 71% | ref. | | ref. | |
| | ILC | 544 | 66% | 0.77 | **0.007** | 0.80 | 0.054 |
| | Other | 270 | 76% | 1.27 | 0.103 | 0.77 | 0.133 |
| | | | | | | | |
| Grade | I | 888 | 64% | ref. | | ref. | |
| | II | 3978 | 71% | 1.38 | **<0.001** | 1.58 | **<0.001** |
| | III | 1778 | 75% | 1.72 | **<0.001** | 1.85 | **<0.001** |
| | Unknown | 27 | 70% | 1.35 | 0.481 | 1.33 | 0.561 |
| | | | | | | | |
| ER | ER+ | 6043 | 70% | ref. | | ref. | |
| | ER- | 585 | 77% | 1.45 | **<0.001** | 1.11 | 0.393 |
| | Unknown | 43 | 84% | 2.17 | 0.062 | 0.50 | 0.133 |
| | | | | | | | |
| Country | Germany | 2802 | 75% | ref. | | ref. | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Italy | 2455 | 77% | 1.13 | 0.066 | 2.62 | **<0.001** |
| | Other | 1414 | 54% | 0.39 | **<0.001** | 0.88 | 0.115 |

ALND = axillary lymph node dissection; pT = pathologic tumor size classification; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; ER = estrogen receptors.

**Figure 1.** Study population: 6,671 T1-2 N0 M0 patients who underwent breast-conserving surgery, had not received neoadjuvant chemotherapy and had a positive sentinel node from 2005 to 2016.

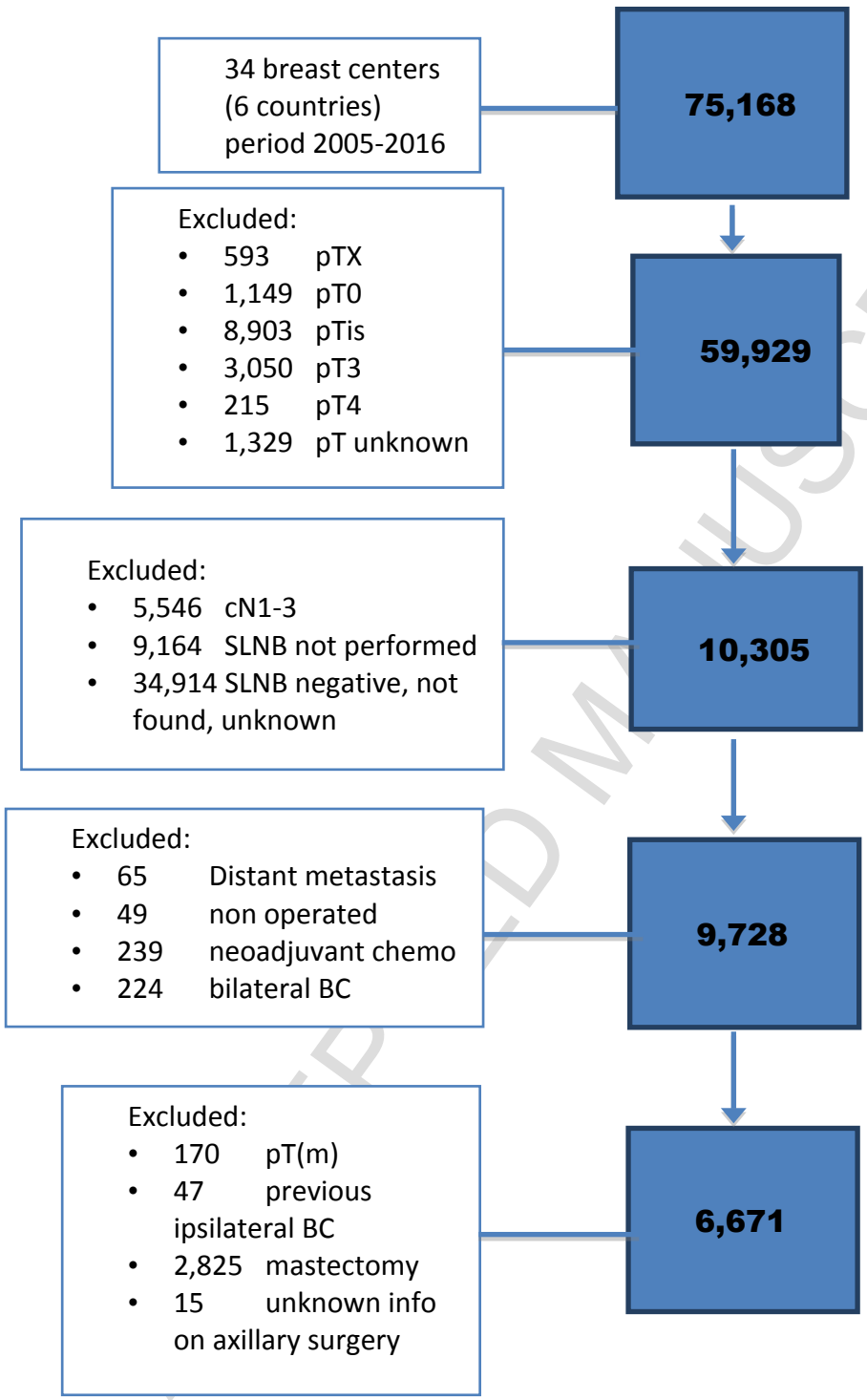
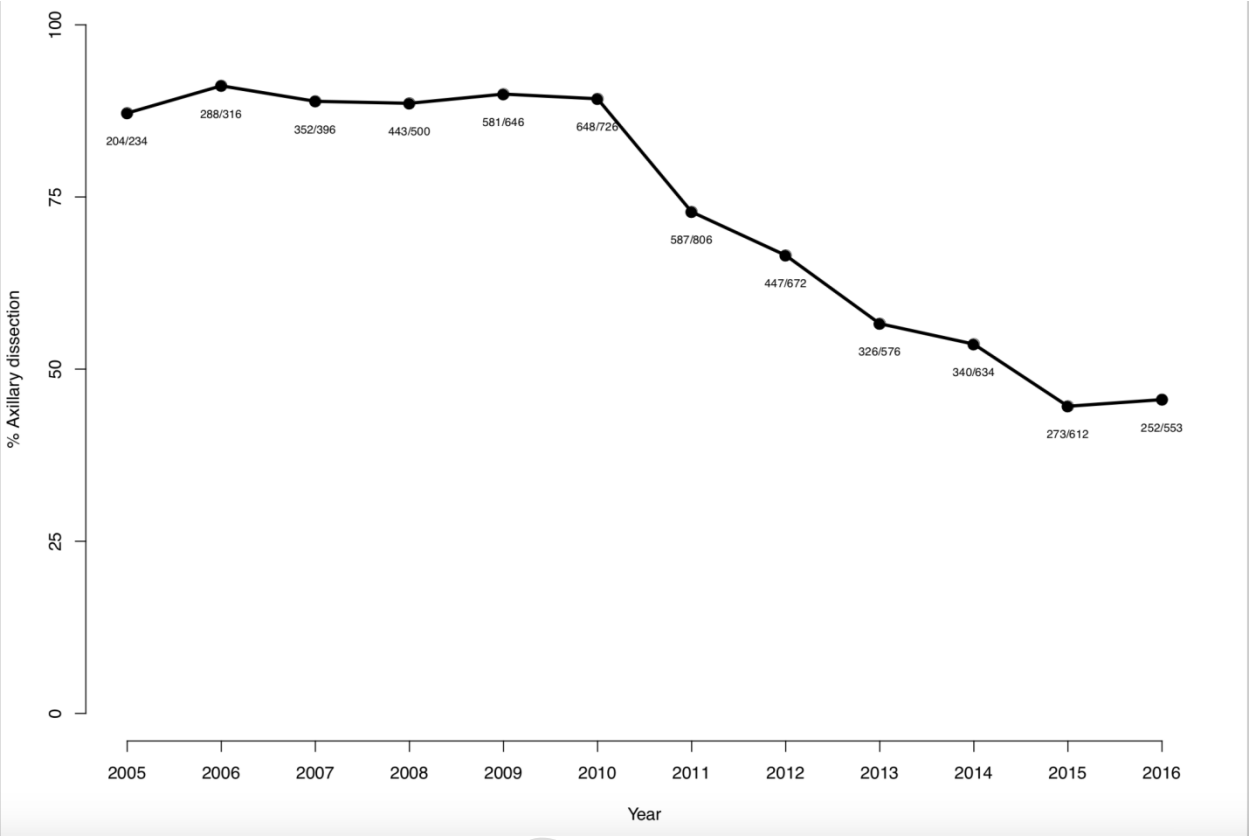
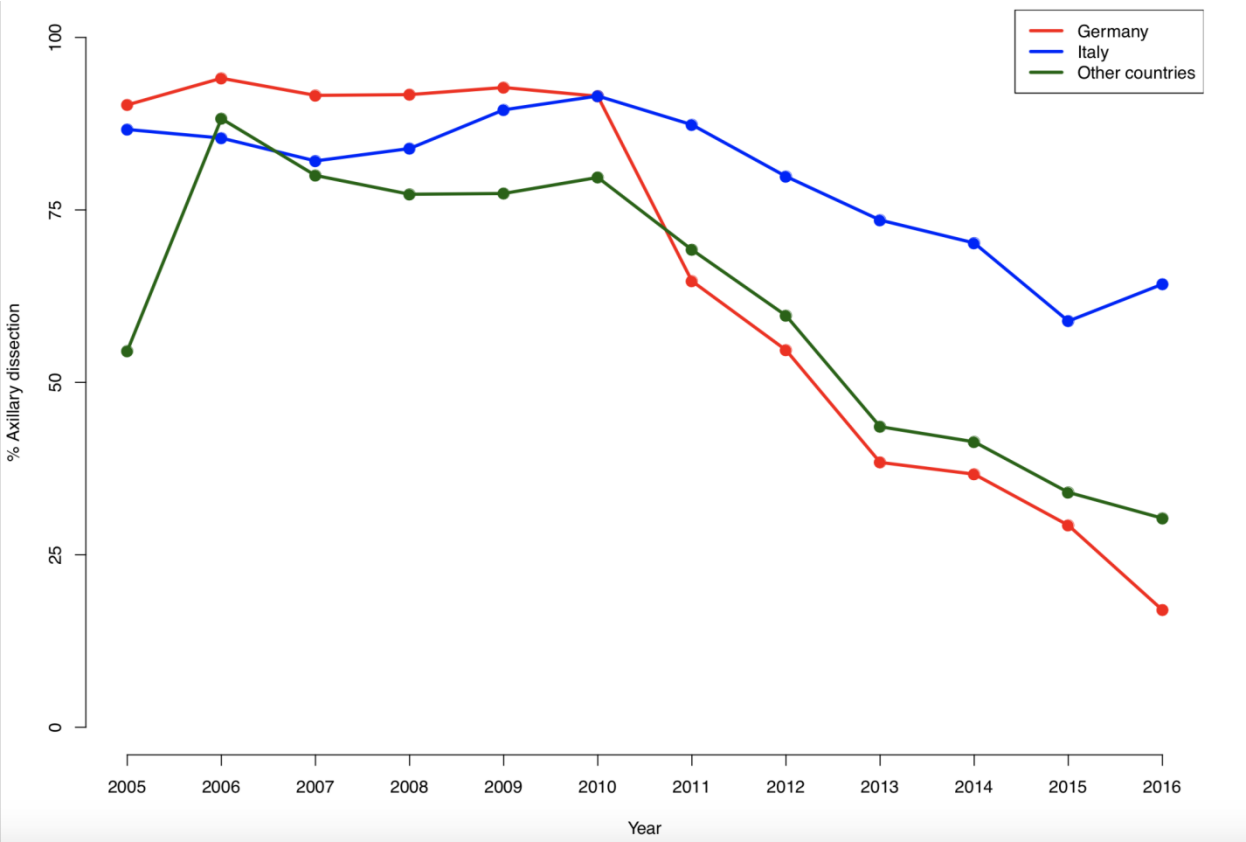


Figure 2. Rates of axillary lymph node dissection from 2005 to 2016 in T1-2 N0 M0 sentinel node positive patients who underwent breast-conserving surgery and had not received neoadjuvant chemotherapy.




chi square test for trend $p < 0.001$

Figure 3. Rates of axillary lymph node dissection by country from 2005 to 2016 in T1-2 N0 M0 sentinel node positive patients who underwent breast-conserving surgery and had not received neoadjuvant chemotherapy.



**HIGHLIGHTS**

- Indications for of axillary dissection in breast cancer have changed based on trials.
- Guidelines for this scenario have been modified in the USA.
- Adoption of these guidelines has been slow and heterogeneous in the USA.
- Little evidence has been reported about change in practice in Europe.
- Axillary dissection rates decreased from 89% to 46% in a European dataset.
- Higher probability of axillary dissection associated with:
    - earlier year of surgery
    - younger age
    - increasing tumor size and grade
    - being operated in Italy
- Minimum and maximal rates of dissection recently reported: 0% and 83% in two centers.
- Wide differences may indicate the need of unified clinical guidelines in Europe.