



## Rates of margin positive resection with breast conservation for invasive breast cancer using the NCDB



Hotsinpiller WJ<sup>a</sup>, Everett AS<sup>b</sup>, Richman JS<sup>c</sup>, Parker C<sup>d</sup>, Boggs DH<sup>a,\*</sup>

<sup>a</sup> University of Alabama at Birmingham, Department of Radiation Oncology, USA

<sup>b</sup> Alliance Cancer Care in Huntsville, Alabama, USA

<sup>c</sup> University of Alabama at Birmingham, Division of Gastrointestinal Surgery, USA

<sup>d</sup> University of Alabama at Birmingham, Division of Surgical Oncology, USA

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### ABSTRACT

**Background:** Previous studies suggest the rate of positive surgical margin (PSM) after lumpectomy for breast cancer is approximately 20 %. The risk of PSM at time of resection is often a source of fear for patients, driving some to elect to undergo mastectomy. This study describes rates and predictors of positive margins for invasive breast cancers in the National Cancer Database (NCDB).

**Materials and methods:** From 2004 to 2013, patients with non-metastatic invasive breast cancers who underwent breast conservation surgery were identified from the NCDB. Patients' demographic, clinical, and facility of treatment characteristics were collected and compared. Per SSO-ASTRO-ASCO criteria, margin negative is defined as no gross or microscopic disease (i.e. no tumor on ink). Bivariate tests and multivariate logistic regression were conducted to identify independent predictors of patients with PSM at the time of resection.

**Results:** A total of 707,798 patients were identified with non-metastatic invasive breast tumors who underwent lumpectomy. Rate of PSM across the entire cohort was 5.02 %. Over time, the rate of PSM decreased significantly from 6.54 % in 2004 to 3.91 % in 2013 ( $p < 0.001$ ). Pure lobular histology predicted for the highest rate of PSM compared with IDC (8.63 vs 4.55 %;  $p < 0.001$ ). In adjusted analysis, high grade, non-ductal histology and HER2 amplification were significantly associated with PSM with breast conservation while estrogen and progesterone status were not.

**Conclusion:** This study demonstrates a 5 % risk of PSM at time of breast conservation surgery using a large, modern national database. Patients with invasive lobular and mixed histology have a nearly two-fold risk of PSM compared to invasive ductal cancers. These results provide important data points to help appropriately counsel patients regarding the risk of PSM.

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## 1. Introduction

Breast cancer remains the most common malignancy among women with recent studies estimating 276,480 new cases of invasive breast cancer diagnosed among women in one year [1]. Treatment options for women with early-stage invasive breast cancer (IBC) may include undergoing total mastectomy or breast conservation therapy (BCT) plus whole breast radiation therapy (WBRT). Multiple randomized phase III trials have shown survival for BCT followed by WBRT to be equivalent to mastectomy for

treatment of stage 1 and 2 (early stage) IBC [2–4]. Since long-term survival is comparable for both therapies, the major benefit of BCT plus WBRT is conservation of as much healthy breast tissue as possible allowing maintenance of a sensate and cosmetically appealing breast. However, a risk to choosing BCT plus WBRT is positive surgical margin (PSM), defined as tumor on ink for IBC, which results in 2-fold increased risk of ipsilateral breast tumor recurrence [5]. As a result, most patients with PSM will undergo re-excision requiring additional surgery, discomfort, health-related costs, and emotional stress.

Of the factors that influence local recurrence, margin resection is one of the few modifiable risk factors, prompting surgeons to seek novel approaches to lower rates of PSM [6]. Previous studies suggest the rate of PSM with BCT plus WBRT is approximately 20 % [7].

\* Corresponding author. Department of Radiation Oncology, University of Alabama at Birmingham, 1700 6th Avenue South, Birmingham, AL, 35249, USA.

E-mail address: [dboggs@uabmc.edu](mailto:dboggs@uabmc.edu) (B. DH).

The risk of PSM at time of resection is often a source of fear for patients, which may be driving many to elect to undergo mastectomy rather than BCT plus WBRT. In fact, recent studies have shown an increase in the rates of mastectomy since the year 2000 [8].

At initial consultation, patients should have appropriate counseling regarding risks of positive margin resection, to aid in treatment decision making. For patients with early stage IBC, it is possible that histology, grade, and receptor status could influence the rate of PSM. With more information about these rates, patients could receive optimal counseling from their oncologists to help in making an informed decision about their treatment plan. The purpose of this study is to describe rates and predictors of PSM at time of resection with breast conservation therapy for early-stage IBC using a large modern patient cohort from the National Cancer Database (NCDB).

## 2. Materials and methods

### 2.1. Study design

From (2004–2013) patients with non-metastatic invasive breast cancers who underwent breast conservation surgery were identified from the NCDB. Our patient cohort included patients with non-metastatic stage (M0 or MX), invasive disease on pathology, and breast conservation surgery with or without radiation treatment (Fig. 1). Patients who received radiation therapy prior to surgery or with unknown margin status were excluded from the analysis. Patients' demographic, clinical, and facility of treatment characteristics were collected for analysis of treatment variables. Patients were stratified by histology, grade, and receptor status. These variables were used to detect predictors for rates of positive margin resections. Per the SSO-ASTRO-ASCO consensus criteria [5], margin negative is defined as no gross or microscopic disease at the margin (i.e. no tumor on ink).

### 2.2. Statistical methods

Using the patient cohort as defined in Fig. 1, patients' treatment

variables were compared using two-sided t-tests and chi-square tests. Multivariate logistic regression was used to identify independent predictors of patients with positive margin at the time of resection adjusting for histology, grade, and receptor status. Odds ratios compared predictors of positive margin, with a p-value of 0.01 defined as statistically significant.

## 3. Results

Between 2004 and 2013, 707,798 patients were identified from the NCDB that met the study criteria. Patient and tumor characteristics are described in Table 1. The rate of margin positive resection across the entire cohort was 5.02 %. Of note, rates of positive margin resection decreased significantly from 6.54 % in 2004 to 3.91 % in 2013 ( $p < 0.001$ ) as shown in Fig. 2.

Lobular histology, histologic grade, and HER2+ receptor status were significantly associated with margin-positive resection with breast conservation. However, estrogen and progesterone status were not significantly associated with margin status. Pure lobular histology predicted for the highest rate of positive margin compared with IDC (8.63 % vs 4.55 %;  $p < 0.001$ ). Mixed histology vs IDC also predicted for positive margin 7.22 % with an odds ratio of 1.57 (95 % CI 1.3–1.91). Her2+ was associated with increased PSM (4.8 % vs 4.1 % OR 1.16). Increasing grade was associated with PSM (Grade 1: 4.0 %; Grade 2: 5.2 %; Grade 3: 5.4 %). Odds Ratio for grade 2 was 1.18 ( $p < 0.03$ ) and grade 3 was 1.29 ( $p < 0.01$ ) compared to grade 1. On multivariable adjusted analysis, grade, histology and amplified HER2 status were significantly associated with PSM while estrogen and progesterone status were not (Table 2).

Increasing clinical T stage at diagnosis was correlated with increased PSM after BCS (T1:4.05 %, T2:6.99 %, T3:18.4 %, T4: 27.4 %,  $p < 0.01$ ) as well as increasing clinical N stage (N0: 4.42 %, N1:7.07 %, N2:10.45 %, N3:11.79 %,  $p < 0.01$ ).

## 4. Discussion

Using a large modern national database, this study demonstrates breast conservation surgery carries only a 5 % risk of positive

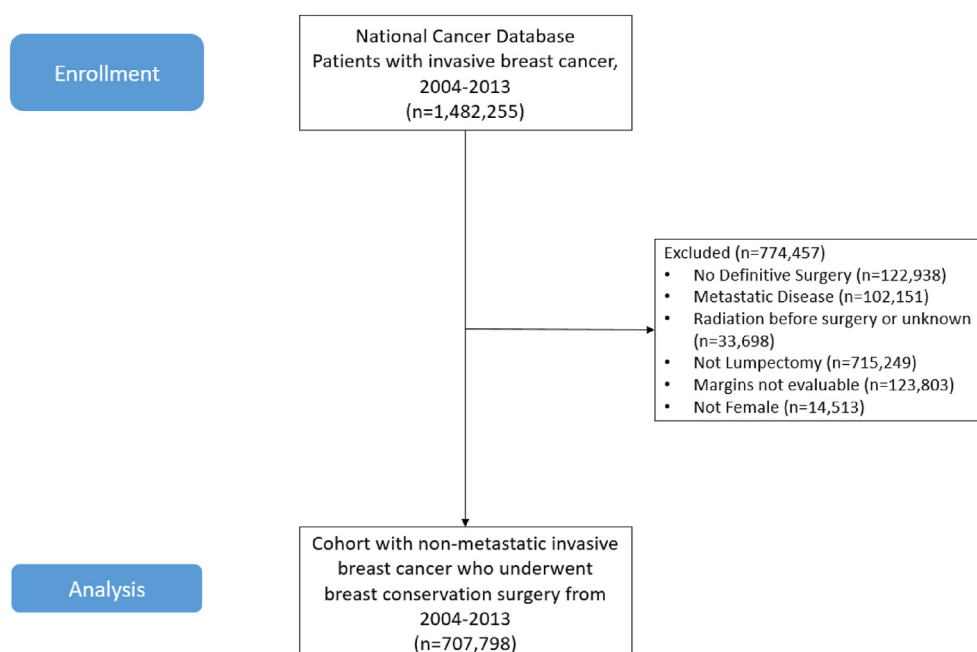
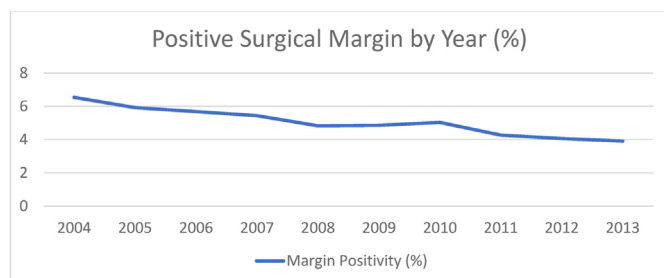


Fig. 1. CONSORT flow diagram.

**Table 1**  
Patient characteristics.

Patient characteristic	Absolute number±1 sd (Percent)
Age	62 ± 12.8
Race	
White	573,316 (81.9 %)
Hispanic	30,081 (4.25 %)
African American	69,364 (9.8 %)
Other	22,366 (3.16 %)
Histology	
Ductal	611,537 (86.4 %)
Lobular	54,430 (7.69 %)
Mixed	41,830 (5.91 %)
Clinical stage	
T1	532,264 (75.2 %)
T2	146,514 (20.7 %)
T3	10,033 (1.46 %)
T4	3610 (0.51 %)
N0	641,264 (90.6 %)
N1	55,491 (7.84 %)
N2	10,616 (1.15 %)
N3	2831 (0.4 %)
Pathologic stage	
T1	543,589 (76.8 %)
T2	174,222 (20.8 %)
T3	6157 (0.87 %)
T4	2194 (0.31 %)
N0	414,770 (58.6 %)
N1	38,929 (5.5 %)
N2	5875 (0.83 %)
N3	1982 (0.28 %)
Grade	
1	174,826 (24.7 %)
2	297,983 (42.1 %)
3	193,937 (27.4 %)
Estrogen receptor	
Positive	586,764 (82.9 %)
negative	121,033 (17.1 %)
Progesterone receptor	
Positive	512,446 (72.4 %)
Negative	196,060 (27.7 %)
HER 2 receptor	
Amplified	95,598 (12.8 %)
Non-amplified	617,200 (87.2 %)



**Fig. 2.** The trend in PSM over time (line graph).

margin resection. This should reassure patients desiring to conserve their natural breast for definitive therapy. Although other studies have described some predictors of margin positive resection, none have the population data described by the NCDB. The large sample size of the NCDB provides additional strength and power of data to the physician in patient counseling [9–14].

Our study demonstrated patients with invasive lobular histology have a nearly two-fold risk of margin positive resection compared to invasive ductal cancers, suggesting its more inconspicuous natural history. This elevated risk supports the use of modern imaging modalities, including US and MRI, for defining the full extent of disease prior to making final surgical recommendations. However, these imaging modalities may necessitate additional biopsies, so it is important to counsel patients regarding pre-operative evaluation modalities, particularly with invasive lobular histology.

Despite the vast majority of lobular carcinomas expressing ER and PR, hormone positivity did not predict for positive margin resection. Patients with HER2 amplification suffer from increased risk of positive margin resection with an OR of 1.12 (95 % CI 1.01–1.24). This may result from the aggressive nature of HER2 amplified disease, or other factors not accounted for in the study design.

Increasing tumor grade also associated with a higher incidence of PSM. Lovrics et al. also demonstrated a correlation with high grade disease and increased risk of PSM, although rates were much higher in their study (23–32 %) than observed in our analysis (4–5.4 %). This may be due to changes in trends of surgical techniques over time, or inherent difficulties of NCDB in capturing first versus repeat surgeries [15].

In our data set, increasing tumor and nodal stage at diagnosis predicted for PSM on univariate analysis. This matches single institution cohort reporting node positive disease, positive lymphovascular space invasion (LVSI) and tumor volume were correlated in PSM [15]. Tarter et al. also found nodal involvement was predictive of PSM on multivariate analysis [16].

Patients with DCIS were purposefully not included in our study. Given the ASTRO-SSO recommendations of a 2 mm margin around disease in DCIS, positive margins alone in the pre-invasive setting would underestimate the number of patients needing re-excision and thus would be less beneficial for patient counseling [17,18].

The limited coding in the NCDB prohibits determining the exact number of excisions to reach negative margins. Regardless, these results are useful information in patient counseling, with large population-based data to support risk factors that may be involved with positive margin resection. Since having a persistent positive margin after surgical excision increases the risk of local recurrence in invasive breast cancer after breast conservation, appropriate expectations and patient counseling is critical for optimizing oncologic and cosmetic outcomes for patients [19,20].

**Table 2**  
Multivariable analysis of predictors of positive margins.

Factor	Odds ratio	Confidence interval (95 %)	P-value
Ductal histology	1.0	(reference)	NA
Lobular histology	1.96	(1.66–2.31)	<0.01
Mixed histology	1.57	(1.3–1.91)	<0.01
Grade 1	1.0	(reference)	NA
Grade 2	1.18	(1.02–1.37)	0.03
Grade 3	1.29	(1.1–1.51)	<0.01
Estrogen receptor positive	1.03	(0.91–1.19)	0.6
Progesterone receptor negative	0.93	(0.83–1.05)	0.26
HER 2 receptor positive	1.16	(1.06–1.29)	<0.01

## 5. Conclusion

This large national database study demonstrates only 5 % risk of positive margin at time of breast conservation surgery. Patients with invasive lobular histology have a nearly two-fold risk of margin positive resection compared to invasive ductal cancers. HER2 amplified disease increases patients' risk of margin positive resection, while grade, estrogen and progesterone status did not significantly predict for positive margin. These results provide important data points to help appropriately counsel patients regarding the risk of positive margins, and possible need for re-excision in patients desiring breast conservation therapy in the modern era.

## Author contributions

WJH, AE, CP, and DHB contributed to the study conception. All authors contributed to design and drafting of manuscript. JR provided statistical expertise. WJH, AE, and DHB made critical revisions to the paper. DHB supervised the submission of the manuscript.

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## Declaration of competing interest

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