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The Role of Intraoperative Pathologic Assessment in the Surgical Management of Ductal Carcinoma In Situ

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Abstract

Background—Re-excision surgeries for the treatment of ductal carcinoma in situ (DCIS) put a strain on patients and healthcare resources; however, intraoperative pathologic assessment of DCIS may lead to a reduction in these additional surgeries. This study examined the relationship between intraoperative pathologic assessment and subsequent operations in patients with a diagnosis of DCIS.

Methods—Surveillance, Epidemiology, and End Results—Medicare patients diagnosed with DCIS from 1999 to 2007 who initially underwent partial mastectomy, without axillary surgery, were included in this study. Use of intraoperative frozen section or touch preparation during the initial surgery was assessed. Multivariable logistic regression was used to describe the relationship between the use of intraoperative pathologic assessment and any subsequent mastectomy or partial mastectomy within 90 days of the initial partial mastectomy.

Results—Of 8259 DCIS patients, 3509 (43 %) required a second surgery, and intraoperative pathologic assessment was performed for 2186 (26 %). Intraoperative pathologic assessment had no statistically significant effect on whether or not a subsequent breast surgery occurred (adjusted odds ratio 1.07, 95 % confidence interval 0.95–1.21; $p = 0.293$). Patient residence in a rural area, tumor size ≥2 cm, and poorly differentiated tumor grade were associated with a greater likelihood of subsequent surgery, while age 80 years and older was associated with a lower likelihood of subsequent surgery.

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Conclusions—The use of intraoperative frozen section or touch preparation during partial mastectomy from 1999 to 2007 was not associated with a reduction in subsequent breast operations in women with DCIS. These results highlight the need to identify cost-effective tools and strategies to reduce the need for additional surgery in patients with DCIS.

There is growing concern that ductal carcinoma in situ (DCIS) is overdiagnosed and overtreated.[1,2] A recent modeling study estimated that 31 % of women over 40 years of age with DCIS or localized breast cancer are treated for disease that would never present clinically in the absence of screening.[3] However, surgery for DCIS is the standard treatment as it is not currently possible to predict which patients with DCIS will progress clinically and which will not. This makes minimizing the burden of surgical treatment a priority for those caring for women with DCIS.

For many women with early-stage breast cancer, partial mastectomy is the preferred treatment. An estimated 21–25 % of these women will have positive margins and will require a re-excision.[4] In a study of the National Cancer Database, 33 % of women who underwent partial mastectomy for DCIS were found to undergo a repeat operation,[5] which indicates an opportunity to minimize the burden of surgical treatment of DCIS for a substantial proportion of women by increasing the likelihood of complete excision at the time of the initial surgery.

Intraoperative pathologic assessment with frozen section or touch preparation allows for the assessment of breast tissue margins at the time of the initial partial mastectomy. Surgeons can use this information to inform intraoperative decision making. Based on such information, surgeons may re-excise additional tissue during the initial operation, potentially preventing the need for a future operation. This study examined the use of intraoperative pathologic assessment for patients undergoing partial mastectomy for DCIS, and sought to identify and measure any potential effect of intraoperative pathologic assessment on subsequent operations in the surgical management of DCIS.

METHODS

Design and Study Population

A retrospective cohort study of women aged 66 years and older, diagnosed with DCIS between 1999 and 2007, was performed utilizing the Surveillance, Epidemiology, and End Results (SEER)—Medicare-linked database. To focus specifically on the management of DCIS, the cohort only included women for whom DCIS was their first and only cancer diagnosis. The study included women who had a partial mastectomy, without sentinel lymph node biopsy or other axillary lymph node dissection, as their initial operation following the diagnosis of DCIS.

The National Cancer Institute and the University of Wisconsin Health Sciences Internal Review Board approved the use of SEER–Medicare data for this study.

Independent Variables

The primary independent variable of interest was a claim for intraoperative pathologic assessment with either touch preparation [Current Procedural Terminology (CPT) codes 88161 and 88329, 88333 and 88334] or frozen section (CPT codes 88331 and 88332), as previously described by Miller et al.[6] All patients included in the cohort had a claim for final pathology (CPT codes 88300–88309). Basic demographic variables included age, race, and location of residence, while disease-related variables included Charlson comorbidity index, diagnosis of overweight or obese, tumor grade, and tumor size. Sixty percent of patients were missing data on estrogen and progesterone receptor status, and no data were available on human epidermal growth factor receptor 2 (HER2) status; therefore, these clinical characteristics were not included as variables. Hospital characteristics were not included as independent variables due to the large number of missing observations (30–65 %), likely attributable to missing data from outpatient surgery centers.

Primary Outcome

The primary outcome of interest was any subsequent surgery for resection of additional breast tissue within 90 days of the initial surgery, including partial mastectomy or mastectomy, with or without lymph node dissection. In the SEER–Medicare dataset, no coding exists to definitively determine whether or not the subsequent surgery was performed to excise positive margins. Therefore, patients who had subsequent mastectomy with reconstruction within 1 year were not included in the study cohort in order to avoid confounding related to preferences for reconstruction instead of breast-conserving surgery once the extent of disease was defined.

Analysis

Univariate analysis used Pearson Chi squared tests to compare patient characteristics for women who did and did not have specimens sent for intraoperative pathologic assessment during their initial surgery. Stepwise multivariable logistic regression analysis was then performed to identify characteristics independently associated with intraoperative pathologic assessment. To identify characteristics associated with subsequent breast cancer resection within 90 days of the initial partial mastectomy, a separate multivariable logistic regression analysis was performed. All statistical analyses were performed in STATA (Stata-Corp. 2013. Stata Statistical Software: Release 13; StataCorp LP, College Station, TX, USA)

RESULTS

A cohort of 8259 women who underwent partial mastectomy for a diagnosis of DCIS was analyzed. The mean age of this SEER–Medicare cohort was 72 years, the majority of the women were White (87 %) and were healthy, and >60 % had a Charlson comorbidity index of 0. Forty-seven percent had low- to intermediate-grade DCIS and 80 % had a primary tumor size <2 cm. Intraoperative pathologic assessment was performed in 26 % of all initial partial mastectomies for resection of DCIS. Of the surgeries that involved intraoperative pathologic assessment, 68 % used touch preparation, 27 % used frozen section, and 5 % used both techniques. Forty-three percent of the overall cohort underwent at least one subsequent surgery within 90 days, either partial mastectomy or mastectomy (Table 1).

On univariate and multivariable analysis, the characteristics of women with DCIS differed only slightly between those who did and did not have intraoperative pathology. Women who had intraoperative pathology for DCIS were significantly more likely to have a tumor grade of 'not otherwise specified' (NOS) (Table 2). Although statistically significant, the clinical significance of these findings is unclear. Variables describing the availability of intraoperative pathology and institutional characteristics had >25 % missing observations; therefore, no clinically significant variables were identified in association with increased or decreased utilization of intraoperative pathology.

Among the women who had intraoperative pathology, 975 (45 %) had subsequent surgery, while among those who did not have intraoperative pathology, 2532 (42 %) had subsequent surgery. The relationship between intraoperative pathology and subsequent surgery was significant on univariate analysis ($p = 0.009$); however, the relationship was not significant after controlling for other factors included in the multivariable model.

The multivariable model of factors related to subsequent surgery after lumpectomy for DCIS demonstrated that age, patient residence, tumor grade, and tumor size were significantly related to subsequent surgery. Age 80 years and older was associated with a lower likelihood of undergoing subsequent surgery. Patient residence in a rural location, poorly differentiated or NOS tumor grade, and tumor size ≥2 cm were significantly associated with undergoing subsequent surgery after the initial partial mastectomy. Intraoperative pathologic assessment did not significantly affect whether or not a subsequent operation occurred after the initial partial mastectomy (Table 3).

DISCUSSION

This study provided informative findings for surgeons, pathologists, health services researchers, and others involved in health systems improvement efforts aimed at making breast cancer care more effective and efficient. Findings demonstrate that routine use of intraoperative pathology with either touch preparation or frozen section is not likely to result in a reduction in rates of subsequent surgery for patients with DCIS. This important information indicates a need to identify other mechanisms or procedures to reduce repeat surgery rates in patients with DCIS.

Intraoperative pathology was utilized in one-quarter of the study population, which is an important finding given the lack of population-level studies on utilization of touch preparation and frozen section. Lower utilization of intraoperative pathologic assessment was expected as its role in assessment of tumor margins has been unclear. In a recent survey of Canadian and American general surgeons, 11 and 18 %, respectively, reported using frozen section for intraoperative assessment of margins, whereas 81 and 88 %, respectively, used intraoperative specimen radiography.[7] In a systematic review of frozen section and touch preparation use in breast-conserving surgery for patients with early-stage breast cancer, the pathology techniques were related to lower rates of repeat surgery (10–11 % after intraoperative pathology vs. 35 % after permanent section alone).[8] Given these findings, and those of other single-institution studies,[9–13] the use of intraoperative pathology was expected to be associated with lower numbers of repeat surgery; however, in this nationwide study of

Medicare patients, intraoperative pathology demonstrated no effect on rates of repeat surgery after partial mastectomy for DCIS.

These findings may have economic implications. According to the 2016 Centers for Medicare and Medicaid Services (CMS) Physician Fee Schedule, Medicare pays an average of $80 (USD) in facility fees for each intraoperative pathologic assessment [Healthcare Common Procedure Coding System (HCPCS) codes 88331–88334]. Although a cost analysis was not included in this study, if the use of intraoperative pathologic assessment does not result in reduced re-excision surgery for DCIS, it may not be cost-effective to utilize frozen section and/or touch preparation analyses for patients undergoing breast conservation.

Reasons for the lack of effect of intraoperative pathology on subsequent surgeries may be related to the nature of DCIS. Studies have shown that women with DCIS, or a DCIS histopathologic tumor component, are at higher risk for needing re-excision compared with women with early invasive ductal carcinoma.[5,12] DCIS has also been shown to be more difficult to detect in surgical margins examined with frozen section[14] and touch preparation.[15] Limitations in the ability of these techniques to detect DCIS, and variation in how the techniques are performed at different institutions, may explain why this SEER–Medicare study did not demonstrate the same relationship between intraoperative pathology and subsequent surgeries compared with previous single-institution studies.

The one factor related to a decreased likelihood of subsequent surgery was age 80 years and older. This finding confirms that of a previous study using the National Cancer Database, which demonstrated that women aged 80 years and older with stage 0–II breast carcinoma were less likely to undergo repeat surgery after partial mastectomy.[5] From a clinical perspective, it is not surprising that older women are less likely to be treated with a subsequent surgery, given that the 5-year rate of recurrence in this age group is fairly low (18 % after partial mastectomy alone, 6 % with the addition of RT).[16] Surgeons may also be more aggressive in their initial resection, or accepting of close or positive margins in elderly patients who are more likely to have multiple comorbidities. It is not surprising that cancer-specific factors associated with more aggressive disease, including tumor size of 2 cm or more and poorly differentiated tumor grade, were associated with increased likelihood of subsequent surgery. The association between an increase in subsequent surgery and patient residence in a rural location was an interesting finding. There is evidence that patients from rural areas may receive more aggressive surgical care due to more advanced disease at the time of diagnosis,[17] concern for lack of follow-up,[18] or limited access to radiation therapy,[19] each of which may explain the increased risk of undergoing additional surgery.

These findings provide a new perspective on risk factors for subsequent surgeries, identifying better targets for patient interventions aimed at decreasing rates of subsequent surgery. For example, an ongoing clinical trial is investigating the effectiveness of intraoperative mammography to obtain a completely resected specimen and reduce re-excision rates.[20] A study of non-invasive optical imaging of tumor margins has showed some potential to lower re-excision.[21] Additionally, the US FDA has approved the MarginProbe system, a device that uses radiofrequency signals to identify positive margins

intraoperatively and demonstrates a modest reduction in re-excision rates for surgeons with greater than average re-excision rates.[22] Our study highlights the importance of pursuing these and other innovations to make breast cancer care as efficient and effective as possible.

There are limitations to this study that should also be discussed. To minimize confounding related to the use of intraoperative pathologic assessment for reasons other than margin assessment (i.e. examination of sentinel lymph nodes), the study population was restricted to patients who only had a partial mastectomy for DCIS without any axillary surgery. Because some patients may undergo subsequent mastectomy, not after positive margins are found but after deciding to pursue breast reconstruction instead of breast conservation, the study also excluded patients who underwent reconstruction within 1 year after partial mastectomy. In an attempt to examine only subsequent surgeries for re-excision of positive margins, only subsequent surgeries within 90 days of the initial partial mastectomy were considered. These restrictive inclusion criteria and the finite window for a subsequent surgery may have resulted in lower estimates of re-excision rates, but provided increased confidence that the reasons for intraoperative assessment and subsequent surgery would be related to surgical margins. As with any study that uses administrative data, the findings of this study may have been limited by coding errors. For example, if excisional biopsies were incorrectly classified as partial mastectomies, the estimated rate of repeat surgery would be higher than that of other studies better able to avoid misclassification of excisional biopsies. This study was also limited by the lack of data on the reason for a subsequent surgery. The restrictive inclusion criteria of the study make it likely that the reason for any subsequent surgery within 90 days was due to close or positive margins during the initial surgery, but other reasons could not be determined. If anything, this would have underestimated the proportion of patients undergoing re-excision, making our conclusions still valid.

Lastly, the use of Medicare claims data limited the scope of this study to women over the age of 65 years. Few national databases collect information on the use of intraoperative pathologic assessment, and Medicare claims tend to capture a nationally representative sample.[6] Given that 40 % of women diagnosed with DCIS in the US are aged 65 years and over,[23] our study likely captured a representative sample to assess the role of intraoperative pathology.

CONCLUSIONS

This study provides information on factors associated with subsequent surgery after partial mastectomy for DCIS in women over the age of 65 years. While intraoperative pathologic assessment with frozen section or touch preparation demonstrated no effect on rates of subsequent surgery, future pre- and intraoperative interventions that address gaps in diagnostic accuracy and risk assessment have the potential to make breast cancer care more efficient through reduction in second surgeries.

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TABLE 1

Characteristics of patients with DCIS who underwent initial partial mastectomy with or without intraoperative pathologic assessment

Characteristics	*N* = 8259[a]	%[b]
Age (years)		
66–69	1991	24
70–74	2379	29
75–79	2079	25
80–84	1288	16
≥85	522	6
Race		
White	7175	87
Non-White	1079	13
Patient residence		
Metropolitan	7302	88
Rural	957	12
Charlson comorbidity index		
0	5288	64
1	1574	19
2	790	10
≥3	588	7
Overweight or obese	1332	16
Tumor grade		
Well-differentiated	1133	14
Moderately differentiated	2667	33
Poorly differentiated	1942	24
Anaplastic	932	12
NOS	1585	18
Tumor size (cm)		
<2	4461	80
≥ 2	1170	20
Intraoperative pathology	2186	26
Subsequent surgery	3509	43

Abbreviations: *DCIS* ductal carcinoma in situ, *NOS* not otherwise specified

[a] Column totals may not add up to the total sample sizes due to missing observations

[b] Percentage totals may not add to 100 % due to rounding

TABLE 2

Multivariable model of factors associated with the use of intraoperative pathologic assessment for DCIS

Variable	Intraoperative pathology [*N* = 2186 (%)][a]	No intraoperative pathology [*N* = 6073 (%)][a]	Adjusted OR for intraoperative pathology	95 % CI	*p* value
Age (years)					0.621
66–69	519 (24)	1472 (24)	Reference		
70–74	653 (30)	1726 (28)	1.08	0.91–1.27	
75–79	564 (26)	1515 (25)	1.11	0.94–1.32	
80–84	326 (15)	962 (16)	1.00	0.82–1.22	
≥85	124 (6)	398 (7)	0.96	0.74–1.26	
Race					0.061
White	1921 (87)	5254 (88)	Reference		
Non-White	265 (13)	814 (12)	0.84	0.71–1.01	
Patient residence					0.399
Metropolitan	1903 (87)	5398 (89)	Reference		
Rural	282 (13)	675 (11)	1.08	0.90–1.31	
Charlson comorbidity index					0.221
0	1418 (65)	3870 (64)	Reference		
1	428 (20)	1146 (19)	1.04	0.90–1.22	
2	184 (8)	606 (10)	0.85	0.69–1.05	
≥3	151 (7)	437 (7)	0.86	0.67–1.09	
Overweight or obese	368 (17)	964 (16)	1.13	0.96–1.33	0.128
Tumor grade					0.003
Well-differentiated	282 (13)	851 (14)	Reference		
Moderately differentiated	686 (31)	1981 (33)	1.08	0.90–1.31	
Poorly differentiated	515 (24)	1427 (24)	1.11	0.90–1.36	
Anaplastic	227 (10)	705 (12)	1.01	0.79–1.28	
NOS	476 (22)	1109 (18)	1.45	1.17–1.80	
Tumor size (cm)					0.326
< 2	1180 (78)	3281 (80)	Reference		
≥2	327 (22)	843 (20)	1.08	0.93–1.25	

Abbreviations: *DCIS* ductal carcinoma in situ, *OR* odds ratio, *CI* confidence interval, *NOS* not otherwise specified

[a]Column totals may not add up to the total sample sizes due to missing observations, and percentage totals may not add to 100 % due to rounding

TABLE 3

Multivariable model of factors related to subsequent surgery after partial mastectomy for DCIS

Variable	Adjusted OR for subsequent surgery	95 % CI	*p* value
Age (years)			<0.001
66–69	Reference		
70–74	0.96	0.83–1.12	
75–79	0.91	0.78–1.06	
80–84	0.74	0.62–0.88	
≥85	0.57	0.44–0.73	
Race			0.305
White	Reference		
Non-White	0.92	0.79–1.08	
Patient residence			0.030
Metropolitan	Reference		
Rural	1.21	1.02–1.44	
Charlson comorbidity index			0.074
0	Reference		
1	1.04	0.90–1.20	
2	0.81	0.67–0.98	
≥3	0.88	0.71–1.09	
Overweight or obese	1.09	0.94–1.27	0.236
Tumor grade			<0.001
Well-differentiated	Reference		
Moderately differentiated	1.06	0.89–1.26	
Poorly differentiated	1.36	1.13–1.63	
Anaplastic	1.02	0.82–1.26	
NOS	1.30	1.07–1.59	
Tumor size (cm)			<0.001
<2	Reference		
≥ 2	2.27	1.98–2.59	
Intraoperative pathologic assessment	1.07	0.95–1.21	0.293

Abbreviations: *DCIS* ductal carcinoma in situ, *OR* odds ratio, *CI* confidence interval, *NOS* not otherwise specified