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Intracystic Papillary Carcinoma of the Breast: A SEER Database Analysis of Implications for Therapy

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Abstract

Background—Intracystic papillary carcinoma (IPC) of the breast is a rare breast malignancy with an indolent course. However, patients can develop metastatic disease. Indications for surgery and radiotherapeutic management have not been well elucidated.

Methods—We identified 2,649 female patients with IPC from the Surveillance, Epidemiology, and End Results (SEER) registry. Differences in demographics, clinical features and survival of patients were assessed using the Kaplan-Meier method and Cox regression.

Results—Median age was 67 years. The majority of patients were white with Stage 0 disease. Most patients had lymph node evaluation and only 34% received radiation therapy. Using a log-rank test, survival was significantly better in Caucasian compared to African-American patients, patients with early stage disease, negative lymph nodes and those who received radiation (all $p < 0.0001$). In a Cox regression survival model adjusting for age, stage and grade, patients who were African-American (hazard ratio [HR] 2.0, CI 1.4–2.8; $p < 0.0001$) had a significantly higher risk of death than Caucasians. Patients who received radiation therapy (HR 0.5, CI 0.3–0.7; $p = 0.0003$) had a lower chance of death than patients that did not undergo radiation.

Conclusion—Overall, IPC has a good prognosis. Survival is improved in Caucasian patients and in patients who receive radiation therapy. Radiation therapy should be offered to women with IPC who undergo breast conserving surgery.

Keywords

Intracystic papillary carcinoma; Breast cancer; SEER

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Introduction

Criteria to distinguish benign papillary neoplasms from papillary carcinomas were first defined by Kraus and Neubecker[1]. Papillary carcinomas were later subclassified into invasive and noninvasive forms[2]. Noninvasive papillary carcinomas may be subdivided into a diffuse form, called the papillary variant of DCIS, and a localized form called encapsulated papillary carcinoma of the breast. Encapsulated or intracystic papillary carcinomas (IPC) commonly occur as a solitary tumor in a cystic and dilated duct[3]. IPCs of the breast are rare tumors accounting for less than 2% of all breast malignancies[4–6]. Typically, they occur in postmenopausal women presenting with a palpable mass, bloody nipple discharge, or on mammography as a round, oval, or lobulated circumscribed mass due to the appearance of the dilated duct rather than the tumor within it[6,7]. Histologically, the tumor is encysted and contains nodules of papillary carcinoma surrounded by a thick fibrous capsule[2,4,6].

In 2012, the WHO Working Group for the 4th edition regarded encapsulated (intracystic) papillary carcinoma as a variant of papillary carcinoma, with absence of myoepithelial cells both within the papillae as well as around the periphery of the tumor[8,9]. This lack of the myoepithelial layer, has led to the hypothesis that IPC may be a relatively less aggressive tumor with expansile invasion, or a minimally invasive form of low-grade carcinoma, rather than a variant of DCIS. Other theories consider IPC to be a tumor in transition from an in-situ to an invasive phase[10–12]. Despite the inconsistencies in establishing the true biological nature of these tumors, given their indolent nature, the WHO working group recommends classifying and treating them as them as Tis (in-situ carcinoma) for staging purposes, unless they have a clearly invasive component[8,13,14].

Axillary lymph node metastases and markers associated with invasion have been documented in patients with even the pure form of IPC[11,15,16]. Due to the rarity of the tumor and variability observed in treatment strategies, only a few studies involving a very small number of patients, have examined the significance of lymph node status and the role of adjuvant therapies[17–19].

We aimed to use a large population-based database to elucidate the outcomes, variations in treatment pattern and survival of patients with IPC.

Methods

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program includes cancer registries covering 28% of the U.S. population[20]. Using the 2012 SEER release, we identified 2,649 female patients with IPC from the SEER registry from 2000–2009. Per SEER, IPC was defined as a variant of intraductal carcinoma used to describe encysted forms of papillary carcinoma. Tumors were coded as in situ unless the histology was described as invasive intracystic carcinoma. Grade was coded per Bloom Richardson or Nottingham score/grade based on Collaborative Stage version 2 site-specific factor 7 (SSF) of the SEER coding guidelines. For patients coded using a 4-tier grading system, grade 4 represented undifferentiated or anaplastic tumors. Staging was done based

on the year of diagnosis with those diagnosed 2000–2003 using AJCC 3rd edition and 2004–2009 diagnosis years using AJCC 6th edition. Patients with a previous diagnosis of breast cancer and male breast cancer were excluded. Demographic and clinical characteristics were examined. Subjects in the database missing complete information were excluded for some of the characteristics analyzed. We assume this to have occurred at random. Estimation and comparison of survival rates between demographic and clinical features were done using the Kaplan-Meier method. A multivariate Cox regression model was created to assess associations of covariates with overall survival. The model included age, race, lymph node involvement, adjuvant radiation therapy, grade, AJCC stage, and surgery type (lumpectomy or mastectomy). All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). The study was exempt from institutional review board approval as it involved the use of a publically available, de-identified database.

Results

Patient characteristics

The number of subjects available for analysis (female subjects with IPC) was 2,649. The median patient age was 67 years (range 20 – 103). The majority (70.1%) of patients were Caucasian (n= 1,842). 89.1 % of patients (n=2,284) had stage 0 or I disease and less than 1% had metastatic disease (n=12) at the time of presentation. 81.9% (n=1417) had low-grade (1 or 2) disease. 90.2% of patients (n=1,268) had estrogen receptor (ER) positive tumors. (Table 1)

Of the patients who had axillary nodal status available, only 5.5% had tumor involvement. Most patients had lumpectomy (n=1,721, 68.2%) and only about one-third received adjuvant radiation therapy (n=897, 34.9%). (Table 1)

Survival

With a median follow-up of 4.8 years, 4-year survival was 89% and 8-year survival was 76.3%. Using the log-rank test, survival was significantly better in patients with negative lymph nodes, lower AJCC stage and for those receiving radiation (all $p < 0.0001$) (Figure 1). Within the lumpectomy group, women that received radiation had improved overall survival compared to those that did not ($p < 0.0001$) (Figure 2). Survival was also worse for African American compared to Caucasian women (Figure 3). In a multivariate Cox regression survival model adjusting for age, stage and grade, patients who were African-American had a significantly higher risk of death than Caucasians (hazard ratio [HR] for death 2.0, CI 1.4, 2.8; $p < 0.0001$). Those who received radiation (HR 0.5, CI 0.3 to 0.7; $p = 0.0003$) had lower risk of death (Table 2). There was no significant difference in survival in patients who received either a lumpectomy or mastectomy (HR 1.0, CI 0.7 to 1.3; $p = 0.8276$) or in patients with positive versus negative lymph node status (HR 1.0 CI 0.6 to 1.8; $p = 0.9166$).

Discussion

This is the largest series in the literature of IPC, with 2,649 cases. IPC is a rare form of breast cancer accounting for fewer than 2% of breast malignancies[6,17,19,21]. Currently, IPC is considered to be a low-grade carcinoma or a tumor in transition from in-situ to

invasive disease.[6,10,12,22–24]. Although less common, axillary lymph node or distant metastases has been noted even without frank invasion[15,19]. Given the rarity of the disease and confusion regarding its histological classification, there is no widespread consensus on the management of patients with IPC. The present study uses a large sample of patients to study the clinicopathological characteristics as well as outcomes and treatment strategies used for patients with IPC.

The median age of patients in the present study was 67 years. Several previous studies have similarly shown that IPC frequently occurs in elderly postmenopausal women[14,17–19,25]. The majority of the patients in this study were Caucasians (70.1%), similar to other studies in the literature[6,17]. Most series including the present, report a high rate of estrogen receptor positivity from 90 to 100% [17,23,25,26]. More than 89% of patients presented with clinically in-situ or Stage I and low grade disease (89.1%) with an extremely low incidence of distant metastases (< 1 %) at the time of presentation, in accordance with other reported series in the literature[6,10,17–19,23,25,26]. Previous studies have correlated ER positivity with proliferative markers like BCL-2 expression, low p53 expression, low nuclear grade and proliferating cell nuclear antigen (PCNA), partly explaining the indolent course of these cancers[27]. Factors such as high nuclear grade, frequent mitotic activity, cyclin D1 and p53 overexpression are associated with stromal invasion and portend a more aggressive clinical course[28]. Although our study did not specifically analyze individual expression of these proliferative and prognostic markers, and we did not have information on use of adjuvant endocrine therapy, the high rate of hormone receptor positivity seen in our study population may indirectly explain the overall excellent survival of patients. Similar correlation of receptor positivity and excellent overall survival for IPC has been noted in several previous published series in the literature[6,17–19,23].

Much of the earlier studies on IPC noted a low rate of concurrent invasive component from 12 to 38% [18,19,21,25]. However, with increasing use of myoepithelial markers and routine excisional biopsy of atypical papillary lesions, more recent studies have shown the incidence of invasive component in IPC to be between 48% and 60% [23,28]. Regardless of whether IPC occurs in its pure form, or accompanied by DCIS or invasion, prognosis remains excellent with almost non-existent lymphovascular invasion[14], a low rate of axillary and distant metastasis and excellent overall long-term survival[17–19,23]. Given the variability of pathological assessment and infrequently performed axillary evaluation, only a few studies have correlated pathological subtype with metastatic potential. Although lymph node involvement is more common in IPC with an invasive component[21,23], some of the studies clearly show occurrence of metastatic disease even in patients with pure IPC[11,15]. None of the studies however specifically correlate lymph node status with survival. In the present study, only 5.5% of patients who underwent assessment of their axilla had lymph node involvement. Patients with a pathologic negative axilla showed better overall survival (Figure 1), but this was not a significant factor predicting death in multivariate analysis. This is likely because of the effect of adjusting for AJCC stage in the model, which incorporates both tumor size and lymph node status. Higher stage patients in the model showed worse survival compared to Stage 0 patients (Table 2). Since detailed histological assessment about whether the patients classified as IPC had pure IPC or the presence of an invasive component are not known, we are unable to draw any definitive conclusions about

significance of lymph node status in patients with IPC. Although we note the lack of uniformity in the approach to the axilla in the management of these patients, we recommend that sentinel node biopsy be performed as node positive patients do have worse prognosis than those with negative nodes.

In one of the earliest studies, Carter et al in 1983 recognized the excellent prognosis of patients with pure IPC. Although 71% of their patients underwent mastectomy, none of the patients developed a recurrence or metastasis; they recommended a more localized excision in favor of mastectomy to treat these patients[2]. In their study of 77 cases, Lefkowitz et al noted a 72% mastectomy rate for their patients[21]. In contrast, most patients (68%) in the present study underwent lumpectomy. This is in accordance with recent trends in increased use of breast conservation for treatment of invasive cancer. Regardless of the surgical procedure, patients undergoing lumpectomy and mastectomy had equivalent survival, a finding which has been reported by others in the literature[2,17–19,23].

Solorzano et al, in their study of 40 patients with IPC noted that one-third (33.3%) of patients received radiation, with no effect of radiation on recurrence free or overall survival outcome[19]. The presence of associated DCIS rather than pure IPC was associated with increased use of radiation. Fayanju et al studied 45 patients with IPC, and noted an overall 61% rate of adjuvant radiation among their patients, with patients that had IPC with DCIS or invasion more likely to be offered radiation compared to those with pure IPC (83% vs 39%) [17]. There was no analysis of survival in the radiation versus the surgery only group. Wynveen et al in their analysis of 39 patients with IPC noted that overall 43.7% of patients received radiation; this included 56.3% of patients that had IPC with invasion as compared to 37.5% of patients with pure IPC or IPC with possible microinvasion. Overall, they were unable to equivocally conclude a benefit from adjuvant radiation, as the number of cases was limited and the original diagnosis tended to favor more aggressive treatment in some patients. In addition, adjuvant hormonal treatments were frequently administered together, making it difficult to discern the specific benefit of radiation alone[23]. In the present study, 34.9% of patients (897/2568) received radiation treatment. Survival of patients who received radiation was improved in comparison to those that did not receive radiation ($p < 0.0001$). When adjusted for age, grade and stage, patients who had radiation treatment were half as likely to die compared to those that did not receive radiation (HR 0.5, CI 0.3 to 0.7; $p = 0.0003$) (Table 2). Although it is not possible to exclude the effects of adjuvant hormonal therapy (as this data is not available), since most patients were ER positive (>90%) and administration of adjuvant hormonal therapy is almost always independent of radiation, one can potentially indirectly infer that the likely benefit of administration of adjuvant hormonal treatment in patients receiving or not receiving radiation treatment was similar. Additionally, adjusting for age, grade and stage which incorporates lymph node status, likely minimizes a significant differential effect of these factors on survival in the patients that received radiation versus those that did not. Importantly, in patients who underwent lumpectomy, survival was improved in patients who received lumpectomy with radiation compared to those that received surgery alone (Figure 2). We therefore feel that in the setting of breast conservation, adjuvant radiation confers a survival advantage in patients with IPC and should be offered to these patients.

Outcomes disparities amongst different races have been studied extensively in patients with invasive breast cancer [29–31]; however no studies to date have analyzed survival outcomes specifically in IPC patients based on race. We noted poorer survival amongst African-American patients, with odds of dying from breast cancer twice that of Caucasians (HR 2.0, CI 1.4, 2.8; $p < 0.0001$) (Table 2, Figure 3). Confounding factors like socioeconomic status and access to healthcare, that may have influenced this outcome, were not included and could potentially bias the observed outcome. However, given the significant racial disparity noted in survival outcome of patients with IPC, which is generally regarded as an indolent tumor with excellent prognosis, our findings have important implications in devising strategies for improved access to treatment as well as evaluation and management of African-American patients with breast cancer.

Our study is limited by the retrospective nature of the analysis using the SEER database and its associated selection bias and missing data. Another limitation was the inability to specifically assess whether patients had pure IPC or the presence of an invasive component. It is certainly possible that given the difficulty in establishing an accurate diagnosis, some of the patients were misclassified or misdiagnosed. Additionally, the effect of administration of other adjuvant therapies could not be assessed as these variables are not captured within the administrative database.

Nonetheless, this is the largest study showing overall excellent prognosis of patients with IPC. Survival was improved in Caucasian women, node negative patients and patients who received radiation treatment. Based on our findings, we recommend offering sentinel node evaluation to all patients and adjuvant radiation to patients with IPC undergoing breast conservation.

Abbreviations

IPC Intracystic papillary carcinoma

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Highlights

- Intracystic papillary breast cancer is a rare cancer with excellent prognosis generally affecting older women
- Survival is better for Caucasian patients, those with lower stage disease and negative lymph nodes
- Radiation therapy may offer a survival benefit in patients undergoing breast conservation

Figure 1.
Survival based on lymph node status

Figure 2.
Survival in patients with lumpectomy

Figure 3.
Survival in patients based on race

Table 1

Patient Characteristics

Variable	n (%)
Mean age (SD) (n=2649)	66 (13.5)
Race (n=2627)	
Caucasian	1842 (70.1)
African-American	409 (15.6)
Hispanic	219 (8.3)
Other	157 (6.0)
Grade (n=1730)	
1	605 (35.0)
2	812 (46.9)
3	253 (14.6)
4	60 (3.5)
ER Status (n=1405)	
Positive	1268 (90.2)
Negative	137 (9.8)
PR Status (n=1370)	
Positive	1121 (81.8)
Negative	249 (18.2)
Surgery Type (n=2523)	
Lumpectomy or partial mastectomy	1721 (68.2)
Mastectomy	802 (31.8)
Radiation Therapy (n=2568)	
No	1671 (65.1)
Yes	897 (34.9)
Lymph Nodes (n=2629)	
No tumor nodal involvement	2485 (94.5)
Lymph node involvement with cancer	144 (5.5)
AJCC Stage (n=2564)	
0	1794 (70.0)
I	490 (19.1)
II	219 (8.5)
III	49 (1.9)
IV	12 (0.5)

SD – Standard Deviation, ER – Estrogen receptor, PR – Progesterone receptor

Table 2

Multivariate Cox regression Model predicting survival

Patient characteristic	Hazard Ratio (95% CI)	p-value*
Age (10 year increase)	1.9 (1.7, 2.2)	<0.0001
Race		0.0005
Caucasian (Ref)		
African-American	2.0 (1.4, 2.8)	<0.0001
Hispanic	1.4 (0.8, 2.4)	0.2904
Other	0.8 (0.3, 1.9)	0.5442
Lymph Nodes		
No tumor nodal involvement (Ref)		
Lymph node involvement with cancer	1.0 (0.6, 1.8)	0.9166
Radiation Therapy		
No (Ref)		
Yes	0.5 (0.3, 0.7)	0.0003
Grade		0.4428
1 (Ref)		
2	0.9 (0.6, 1.2)	0.4024
3	1.0 (0.6, 1.5)	0.8909
4	1.5 (0.8, 3.1)	0.2347
AJCC Stage		<0.0001
0 (Ref)		
I	2.2 (1.6, 3.0)	<0.0001
II	1.7 (1.1, 2.7)	0.0275
III	4.3 (2.1, 9.1)	<0.0001
IV	4.6 (1.1, 19.1)	0.0381
Surgery Type		
Lumpectomy or partial mastectomy (Ref)		
Mastectomy	1.0 (0.7, 1.3)	0.8276

* Bold represents statistically significant values