Breast Cancer Research and Treatment (2020) 182:317–323
https://doi.org/10.1007/s10549-020-05680-9

CLINICAL TRIAL

Intracystic papillary carcinoma: clinical presentation, patterns of practice, and oncological outcomes

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Received: 11 February 2020 / Accepted: 9 May 2020 / Published online: 28 May 2020

Abstract

Background Intracystic/encapsulated papillary carcinoma remains a poorly understood disease of the breast with a little amount of reports that describe it. It shares features with DCIS and IDC and predominantly affects postmenopausal women. This study aims to evaluate the clinical presentation, treatment, and outcomes in IPC patients managed at our institution.

Methods We retrospectively pooled twenty-eight IPC patients' medical records at our institution. Descriptive analysis of clinicopathological characteristics, approach, and outcomes was done along with a quantitative statistical analysis.

Results Cases were divided into three groups: isolated IPC, IPC associated with DCIS, and IPC associated with Invasive Carcinoma. Treatment modalities varied according to the IPC type and its associated components. All patients presented with a palpable mass. Immunohistochemical staining revealed that all isolated IPCs were ER and PR positive and HER2 negative. Lymph node dissection proved necessary only in IPC associated invasive carcinoma. Irregular borders and lobulations, among others, were found on non-invasive core biopsies that turned out to be associated with invasion on surgical pathology. All patients were alive after a median follow-up time of 23 months when the study was over with no reports of recurrence.

Conclusion IPC cases and treatment approaches at our institution appear similar to the available literature and confirm the excellent prognosis among IPC. Even more, further studies into the key features such as BMI, family history, and radiological findings are necessary for a potential algorithm that could assess for risk of finding invasion in surgical pathology and subsequently the need for axillary/sentinel lymph node biopsy.

Keywords Intracystic/encysted papillary carcinoma · Pure IPC · IPC with associated DCIS · IPC with associated invasive carcinoma

Abbreviations

AUBMC	American University of Beirut Medical Center
IPC	Intracystic papillary carcinoma
DCIS	Ductal carcinoma in situ
IDC	Invasive ductal carcinoma
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2
SLNB	Sentinel lymph node biopsy
INV	Invasive
ALND	Axillary lymph node dissection

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Background

Intracystic/encysted papillary carcinoma (IPC) is a rare and peculiar malignancy of the breast, accounting for less than 2% of all breast cancers, and predominantly affecting postmenopausal women [1, 2]. Initially described by Carter et al. as one of two forms of non-invasive papillary carcinomas, IPC remains to this day a relatively poorly understood neoplasm, sharing features with both ductal carcinoma in situ (DCIS; a common type of non-invasive breast cancer) and invasive ductal carcinoma (IDC; the most common type of breast cancer) [3]. In addition, different states of IPC occurrence should be distinguished as follows: an isolated well-defined lesion, in conjunction with DCIS, or as a precursor lesion to invasive carcinoma [4, 5].

Because of the variety of presentations and complex associations of IPC, follow-up data are generally difficult to interpret, and management guidelines are relatively insufficient. Nevertheless, the general consensus is that IPC is primarily a surgical disease with excellent prognosis given adequate excision with negative margins, a behavior consistent with that of ductal carcinoma in situ. In the presence of a more advanced lesion, namely poorly delineated DCIS involving surrounding ducts, or secondary invasive carcinoma, treatment would be planned according to the associated neoplastic process. When isolated however, the role of lymph node evaluation through sentinel lymph node biopsy and the contribution of adjuvant therapy to outcome remain unclear. In addition, intracystic papillary carcinoma of the breast can have, in some cases, certain features that may help through a multidisciplinary approach to predict its associated invasive risk. As such, we try to shed light on relevant findings in the patient's demographics, pre-op pathology specimen, and radiological imaging to assess for the risk of an associated invasive cancer and the subsequent prediction of the need for axillary staging by sentinel lymph node biopsy (SLNB). The aim of this study is to shed more light on the clinical presentation, current management practices, and oncological outcomes of IPC patients treated at our center.

Methods

The study was approved by our hospital's Institutional Review Board. Patients' informed consent was waived as permissible under the 45 CFR 46.116 subpart of the HHS regulations. A total of 28 patients representing 29 cases with a diagnosis of intracystic papillary carcinoma were identified between January 1, 1996 and March 30, 2018. The medical records of all patients were retrieved from the Electronic Health Records system at AUBMC and then retrospectively reviewed. Pathology findings, radiology reports, and treatment approaches of each patient were recorded. The 28 patients were divided into three groups: isolated IPC, IPC associated with DCIS, and IPC associated with invasive carcinoma.

Descriptive analysis of pathological and clinical characteristics, treatment modalities, and patient outcomes was performed. Statistical analysis was done using SPSS version 24.0 (SPSS, Inc, Armonk, NY).

This study and manuscript are prepared in accordance with the STROBE statement guidelines for reporting observational studies [6].

Table 1 Study population characteristics

Median age (range), years	59 (34–83)
Median IPC size (range), cm	2 (0.2–6)
Family history of breast cancer	11 (45.8)

IPC intracystic papillary carcinoma

Table 2 IPC staging and tumor necrosis in study population

Stage	*N* (%)
0	13 (44.8)
I	9 (31)
II	6 (20.7)
III	1 (3.4)
Tumor necrosis	*N* (%)
Yes	4 (13.8)
No	25 (86.2)

Results

Clinical and pathological findings

A total of 29 cases of IPC were identified in 28 patients. One patient was diagnosed twice with IPC, each time in a different breast and within a 7-year interval. The median age at presentation was 59 years (range 34 to 83 years). Twenty-five (89.3%) patients were female, and three patients (10.7%) were male. The median tumor size was 2 cm (range 0.2 cm to 6 cm). All patients had a palpable mass at presentation. Pathologic evaluation revealed that 8 patients (27.6%) had pure IPC, 5 patients (17.2%) had IPC with associated DCIS, and 16 patients (55.2%) had IPC associated with invasion. Eleven (37.9%) patients had a positive family history of breast cancer. Patient characteristics and tumor pathological findings are summarized in Tables 1 and 2.

When size-stratified by associated tumors, pure IPC had a median size of 1.9 cm (1.2 cm to 4 cm), IPC with associated DCIS had a median size of 1.85 cm (1 cm to 3 cm), and IPC with associated invasion had the largest median size, 2.4 cm (0.2 cm to 6 cm). The most common stage at presentation was stage 0 disease (44.8%). Estrogen receptor (ER) immunohistochemical staining was performed in 7 patients with pure IPC, 3 patients with IPC and DCIS, and 16 patients with IPC and invasion. All 7 patients with isolated IPC were ER positive. For IPC with associated tumors, ER was positive in 11 IPC patients with associated invasive carcinoma and 1 patient with IPC associated with DCIS. Interestingly, all IPC associated with invasive carcinoma were HER2 (human epidermal growth factor receptor 2) negative. All isolated IPCs were ER/PR positive and HER2 negative.

Molecular subtype in IPCs associated with invasion was either luminal A (ER/PR+, Her2−) or triple negative. Eleven patients (68.8%) had luminal A tumors, while 5 patients (31.3%) had triple negative tumors. The majority of IPCs with associated invasion were grade 2 (46.2%), followed by 38.5% grade 1, and 15.4% grade 3. For IPC associated with DCIS, 66.7% were grade 3, and 33.3% were grade 1. We have data on the grade of 4 IPC tumors, two are grade 1 and two are grade 2. There are 3 patients with tumor necrosis; all are of the IPC type associated with tumors. Patient characteristics and pathologic characteristics of tumor-associated IPC are summarized in Tables 3 and 4.

Treatment and outcomes

The two surgical approaches for breast lesions were done in equal number of patients. Partial mastectomies were done on four (13.8%) isolated IPC patients, six patients (20.6%) with IPC associated with invasive carcinoma, and five (17.2%) with IPC associated with DCIS. Furthermore, total mastectomy was done in two (33.3%) isolated IPC patients, ten (62.5%) IPC patients associated with invasion, and one (25%) IPC associated DCIS patients. Three patients diagnosed at our institution were lost to follow-up and as such were not accounted for in this study. Eight (30.8%) patients underwent full axillary lymph node dissection (ALND), and three of them (13.6%) had positive nodes. On the other hand, fourteen (53.8%) patients underwent sentinel lymph node biopsy (SLNB) all of which were negative. All three patients with positive nodes had IPC associated with invasion. Three patients (10.3%) received adjuvant chemotherapy, all of them having IPCs associated with invasion. Ten patients (37%) received radiotherapy. Among the thirteen patients who underwent partial mastectomy, radiation therapy was given to 8 (isolated IPC: 1/4, 25%, IPC + INV: 5/6, 83%, IPC + DCIS: 2/3, 66%). Eight patients (29.6%) received hormonal therapy, all of them being IPC with associated invasion.

No recurrence was recorded in any of the patients on follow-up. The median follow-up time was 23 months (range of 0 to 124 months). No deaths in the study population were reported by the end of study follow-up period. The treatment and outcomes are summarized by type of IPC in Tables 5 and 6.

Discussion

Intracystic (encysted) papillary carcinoma has garnered a lot of academic attention because of its peculiar morpho-histological character as well as its frequent association with the morphologically distinct yet intimately related DCIS and invasive ductal carcinoma. Much of the controversy surrounding IPCs stems from the fact that, unlike classical DCIS, they seem to lack evidence of myoepithelial cells surrounding the neoplastic proliferation [7, 8]. Just like DCIS however, they give rise to non-specific invasive ductal carcinoma, generally without any evidence of a papillary pattern. This lack of clarity regarding their exact biology, and the unpredictability of their associations make the task of establishing guidelines for management quite challenging. It appears that the majority of these lesions tend to follow

Table 3 IPC types (stratified by association): study population age and family history

IPC type (number of cases)	Pure IPC ($n=8$)	IPC + INV ($n=16$)	IPC + DCIS ($n=5$)
Median age (range), years	64 (34–80)	53 (37–83)	68 (66–75)
Family history of breast cancer	2	7	2

IPC intracystic papillary carcinoma, *INV* invasive carcinoma, *DCIS* ductal carcinoma in situ

Table 4 IPC types (stratified by association): size and pathology

IPC type (number of cases)	Pure IPC ($n=8$)	IPC + INV ($n=16$)	IPC + DCIS ($n=5$)
Median IPC size (range cm)	1.9 (1.2–4)	2.4(0.2–6)	1.8 (1–3)
Grade			
1	2	5	1
2	2	6	0
3	0	2	2
Necrosis			
Yes	0	1	2
No	8	15	3
ER positive	7	11	1

IPC intracystic papillary carcinoma, *INV* invasive carcinoma, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor

Table 5 Study population: management and outcomes

Variable	*N* (%)
Surgical management	
Partial mastectomy	13 (50)
Total mastectomy	13 (50)
Axillary dissection	
No surgery	4 (15.4)
SLNB	14 (53.8)
ALND	8 (30.8)
Patients with positive nodes	3 (13.6)
Non-surgical management	
Adjuvant chemotherapy	3 (10.3)
Radiation therapy	10 (37)
Hormonal therapy	8 (29.6)
Outcomes	
Recurrence events	0 (0)
Death events	0 (0)

SLNB sentinel lymph node biopsy, *ALND* axillary lymph node dissection

Table 6 IPC Types (Stratified by Association): Management and Outcomes

	Pure IPC *N* (%)	IPC + INV *N* (%)	IPC + DCIS *N* (%)
Number of cases	8 (27.6)	16 (55.2)	5 (17.2)
Surgical management			
Partial mastectomy	4 (50)	6 (37.5)	3 (75)
Total mastectomy	2 (33.3)	10 (62.5)	1 (25)
Axillary dissection			
No surgery	2 (33.3)	0 (0)	2 (50)
SLNB	3 (50)	10 (62.5)	1 (25)
ALND	1 (16.7)	6 (37.5)	1 (25)
Patients with positive nodes	0 (0)	3 (18.8)	0 (0)
Non-surgical management			
Adjuvant chemotherapy	0 (0)	3 (18.8)	0 (0)
Radiation therapy	1 (14.3)	7 (43.8)	2 (50)
Hormonal therapy	0 (0)	8 (50)	0 (0)
Partial mastectomy, received radiation therapy	1	5	2
Outcomes			
Recurrence events	0 (0)	0 (0)	0 (0)
Death events	0 (0)	0 (0)	0 (0)

IPC intracystic papillary carcinoma, *INV* invasive carcinoma, *DCIS* ductal carcinoma in situ, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection

an indolent clinical course, with very low rates of recurrence and fatal outcomes [9]. As the biology and epidemiology of breast tumors is not necessarily reproducible across ethnicities and geographic locations, we were interested in describing our experience with IPCs, and how it compares to what has been reported in the literature so far.

The study of the 28 cases that presented at our institution revealed isolated IPC in 8 patients, IPC with associated invasion in 16 patients, and IPC with associated DCIS in 5 patients. All patients had a palpable mass at presentation, which is similar to other reports on the clinical presentation of IPC [10]. Our study population's ages ranged from 34 to 83 years, with a median of 59 years, reflecting the greater incidence of this tumor among older women, which is similar to the literature [11]. This contrasts with the significantly lower mean age of presentation of non-specific invasive breast cancer in our population (approximately 50 years) [12]. It is also worth noting that IPC is relatively more likely to affect male patients than ductal carcinoma, and this is reflected in our study sample with 3 of the 28 patients being males (10.3%). This is contrasted with merely 1% of breast cancer cases worldwide affecting male patients.

The median size of the IPC in our study population was 2 cm. The size for each variant of IPC did not vary significantly, with a median of 1.9 cm for pure IPC, 2.4 cm for IPC associated with invasive cancer, and 1.8 cm for IPC associated with DCIS. The trend was however that the largest intracystic papillary carcinomas were predictably those more likely to be associated with invasion, similar to other reports in the literature [2, 4, 8]. Moreover, larger tumor size was correlated with a higher grade. IPCs with associated invasive or in-situ disease were mostly high-grade tumors, while all of the pure IPCs were low grade. The presence of necrosis was also seen in IPCs with associated tumors. Our study sample and findings are similar to those of Leal et al. [8] who reviewed 29 cases of IPC and found that IPCs are usually of low grade distributed into 37.9% grade 1 and 55.2% grade 2 tumors. Their findings showed that IPCs with low grade have a better prognosis than those with high grade and necrosis.

Although treatment recommendation for IPC is not well established, partial mastectomy, when feasible, is the surgical method of choice in many cases. Indeed, almost half the patients in our series underwent partial mastectomy (44.8%) with favorable outcome. Previous studies confirm the approach, that total mastectomy is not necessary for the treatment of pure IPC [2, 4]. SLNB was performed in roughly half of our patients (53.8%), while 30.8% underwent ALND, and a minority did not undergo axillary evaluation. This was both sufficient to rule out nodal involvement and prove similar to reports that show that SLNB is an appropriate method to evaluate the axilla of patients with IPC, and represents a good alternative to ALND [2, 13].

In our study, 8 (30.8%) patients underwent ALND, three of whom had lymph node metastasis. The patients with positive lymph nodes were all cases of IPC associated with invasive carcinoma (Tables 5, 6) and all three received adjuvant

chemotherapy. Our findings regarding positive nodes on patients are similar to those of Solórzano et al. [2]. In their 2002 series, Solórzano et al. [2] reviewed the charts of 40 patients with IPC and found that 11% of patients who underwent axillary dissection had positive nodes and noted that all had IPC associated with invasion.

In our series, the majority of IPCs with associated tumors received adjuvant radiotherapy (42.8%), while only one isolated IPC patient received adjuvant treatment with radiation. For IPC with associated invasive tumor, 50% of the patients received hormonal therapy, and 43.8% received radiation therapy. This is in accordance with studies that indicate that adjuvant radiation is not required for isolated IPC but is given to IPC associated with invasive or in-situ tumors. A retrospective review by Fayanju et al. [1] on the management of IPC found that patients with IPC and DCIS or micro-invasion were more likely to be treated with adjuvant radiotherapy than patients with isolated IPC.

The variety of treatment approaches in our series and in the literature raises the question of whether IPC management can be standardized. This can be achieved in non-isolated IPCs by treating the associated lesion diagnosed on the biopsy or excision specimen, therefore managing in-situ and invasive carcinoma as dictated by the standard of care and independent of their association with IPC. From our series, it appears difficult to predict whether a patient can be spared sentinel lymph node sampling if the breast biopsy shows no evidence of invasion. One may argue against sentinel lymph node biopsy in small tumors with a low nuclear grade, but our series revealed grade 1 lesions with a size less than 1 cm associated with invasion in 13% of the cases. Suspicious radiographic findings may be of use in this context, as well as generous, mammotome-assisted biopsies that may give the pathologist a full picture of the nature of the lesion at hand [14, 15].

In our study, there were no recurrence or death events, after a median follow-up of 23 months. This is similar to other reports that showed excellent prognosis and low recurrence rates in IPC patients. In their study, Solórzano et al. [2] reported 13 patients (32.5%) with recurrence after a median follow-up of 58 months. Leal et al. [8] had a median follow-up of 42 months and reported one case of local recurrence in a patient who was treated with lumpectomy alone. The recurrence was identical to the original tumor and lacked either in-situ or invasive carcinoma. One patient who had an associated invasive carcinoma died of distant metastasis, but without pathologic confirmation of the recurrent tumor.

Although IPC shows a high propensity for concomitant in-situ and invasive carcinoma, it seems to maintain an excellent prognosis across research reports [10]. We believe this is in part due to the clinical detectability of these lesions and their almost universal presentation as palpable masses. When invasion co-occurs with IPC, it tends to account for only a minor part of the entire lesion, resulting in a predominance of low stage tumors, as in our series (86% T1 or less, 10% node positive disease).

We examined the 15 cases that had foci of micro-invasion, associated invasive ductal or papillary carcinoma on the surgical pathology. Three patients had missing biopsy readings from the charts because the first diagnosis was done at a different institution. The remaining 12 cases were divided as follows: 6 were diagnosed with invasive carcinoma or micro-invasion, 2 with Pure IPC, 1 with DCIS-associated IPC, 1 with DCIS, and 1 with both DCIS and IDC on biopsy reading (Table 7).

It can be noted in the radiological imaging data collected in our series from mammographs and ultrasounds that regardless of the type of IPC on core biopsy, there can always be at least one aberrant feature on either imaging modality associated with the eventual pathological diagnosis of invasion. Micro and macro calcifications, micro and macro lobulations, irregular, hazy and thickened borders, and cystic septations as well as the invasion of the chest wall, such as pectoralis muscles, can be seen in cases where core biopsy failed to coin a diagnosis of invasion, but final pathology did. Speer et al. [15] reports that their study did not identify radiological characteristics to differentiate between non-invasive and invasive intracystic papillary carcinoma. However, they do report some common findings associated with one type of IPC or another such as the finding of an irregular mass on imaging is more often found in a diagnosis of invasive IPC. This further supports our findings and thus can stipulate that combining the imaging findings from the two modalities of mammography and ultrasound may guide the surgeon to the associated risk of invasion with IPC.

In our 15-case series, the smallest tumor to show an aspect of invasive carcinoma or micro-invasion on final pathology was 1.4 cm and the largest 5 cm with a median size of 2.9 cm. Literature search for IPC tumor size revealed that size can only weakly correlate with the malignant potential of the lesion [16]. Nevertheless, lesions reported in the literature to have a malignant or invasive component range between 0.5 and 2.6 cm [16, 17]. These findings and reports warrant hypothesizing that pathologists' and radiologists' specimen's interpretation may confound a correlation between lesion size and malignant potential. It has been found that the actual concordance between pathologists' readings and consensus-derived reference diagnosis was only 75.3% (95% CI 73.4–77.0%; 5194 of 6900 interpretations) [18].

Moreover, we have noted that patients with a pre-op diagnosis of Pure IPC or IPC with associated DCIS and a post-op pathology of associated invasive carcinoma were all overweight or obese with a median BMI of 32 and 25, respectively. There are no reports in the literature correlating weight with an associated invasion for IPC, which

Table 7 Variables for IPC cases with invasion on final pathology

Pre-op core biopsy	Missing biopsy (3)	Pure IPC (2)	IPC/DCIS (2)	DCIS (1)	DCIS/IDC (1)	Invasive (6)	Total (15)
Demographics							
Median age (range)	58 (54–75)	(43–71)	(54–66)	(50)	(51)	43 (37–59)	51 (37–75)
Average BMI	N/A	32.585	25.01	N/A	24	27.87	28.17
Male:female ratio	1:2	0:2	1:1	0:1	0:1	1:5	3:12
Family history of breast cancer							
Positive	0	0	0	0	1	5	6
Tumor size on mammography							
Number of tumors assessed	1	1	2	1	1	2	–
Median size (range, cm)	2.0 cm	2.8 cm	2.4 (1.4–3.4, cm)	2.0 cm	3.8 cm	4 (3–5, cm)	2.9 (1.4–5, cm)
Ultrasound features							
Septation	–	–	–	–	1	1	–
Lobulation	–	1 (micro)	1 (micro)	1 (macro)	–	1	–
Hazy border	–	–	1	–	–	–	–
Irregular border	1	–	–	–	–	1	–
Invading chest wall	–	1 (pectoralis)	–	–	–	–	–
Mammography features							
Calcifications	–	–	1 (micro)	–	1 (coarse)	–	–
Core biopsy							
Microinvasion on core	–	–	–	–	–	3	–
Surgical lymph nodes assessment							
Positive nodes	0	1	0	0	0	6	–

IPC intracystic papillary carcinoma, *DCIS* ductal carcinoma in situ, *IDC* invasive ductal carcinoma, *BMI* body mass index

makes this a key finding to be further investigated in larger study populations.

All cases with an invasive carcinoma or micro-invasion on core biopsy had a positive family history for breast cancer. All male cases and three female cases presented with this history. Literature on the significance of breast cancer family history in patients with IPC is rare. The only reference to family history of breast cancer that we found was in a few case reports, mainly for male patients with IPC [19–21]. This may warrant a meta-analysis to assess for the significance of breast cancers in families with IPC occurrence in male subjects.

All male patients in our series (3 cases) had a surgical pathology finding of invasion, while on core biopsy 1 case IPC with associated DCIS, 1 with an invasive component, and the last had missing biopsy data. Thus, 10% of all IPC cases and 20% of the cases that had a final pathology reading of invasion were male patients. IPC is a rare occurrence in the male gender and with excellent prognosis [21]. Misdiagnosis or missing an IPC in the male population with breast cancer can be one explanation for this discrepancy.

In addition, the male average age at diagnosis with IPC, in this series, is 61 as compared to that reported in the literature which is 70 years [22]. In the female counterpart, the age distribution does not appear to correlate with the finding of invasion on surgical pathology as noted in the 12 female cases with an age range spanning between 37 and 75.

Conclusion

In conclusion and despite its limitations, our study highlights the approach to IPC at our institution, which reveals congruence to the available literature. We also confirm the excellent prognosis among IPC patients, consistent with the reported literature. Conducting a meta-analysis of the available literature on IPC can make way for standardization and easy access to guidelines for the evaluation and management of this rare breast cancer.

Acknowledgements The authors acknowledge the contribution of Mr. Mohamad Wehbe who was involved in this research under the Medical Research Volunteer Program (MRVP) at the American University of Beirut.

Funding This research study was not funded.

Data Availability All data and materials used for this research study will be available upon formally submitting a request to the principal investigator.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no no conflict of interest.

Ethical Approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of the American University of Beirut approved this study.

Informed Consent The requirement for consent was waived as permissible under the 45 CFR 46.116 subpart of the HHS regulations. The manuscript does not contain any individual person's data in any form (detail, image, or videos) that could jeopardize patient's confidentiality. The need for consent was waived because the data collected were through a retrospective chart review.

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