

# Pathologic T1 and T2 encapsulated invasive carcinomas arising from mucinous cystic neoplasms of the pancreas have favorable prognosis and might be treated conservatively

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## Abstract

Carcinoma arising from a mucinous cystic neoplasm (MCN) of the pancreas is termed MCN with associated invasive carcinoma (MCN-AIC) in the fifth WHO classification of digestive tumors (2019). The prognosis of this malignancy varies depending on the relationship of the invasive carcinoma to the cyst capsule, but limited data are available. This study identified 165 surgically resected MCNs including 15 MCN-AICs from a single center between 2008 and 2018 and analyzed their clinicopathologic features. The results confirmed that non-invasive MCNs were completely cured by surgery. All MCN-AICs showing an encapsulated invasion pattern (defined as invasive carcinoma limited to the ovarian-type stroma, cystic septa, and capsule) had an excellent prognosis with a 5-year survival rate of 100%, even when the size of the invasive component was up to stage T2. By contrast, MCN-AICs with extracapsular involvement had unfavorable clinical outcomes. Our study demonstrates that the pattern of invasion of MCN-AIC can predict patient prognosis. Pathologic stage T1 and T2 encapsulated MCN-AICs may be completely cured with surgical resection alone or when combined with postoperative chemotherapy.

**Keywords:** mucinous cystic neoplasm; pancreatic cancer; pancreatic adenocarcinoma; invasive carcinoma; T1 pancreatic cancer; T2 pancreatic cancer; prognosis; prognostic factor

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## Introduction

Mucinous cystic neoplasm (MCN) of the pancreas is a cystic, mucin-producing neoplasm primarily located in the body and tail of the pancreas and that occurs almost exclusively in middle-aged female patients. Compagno and Oertel [1] first distinguished MCN from serous cystic neoplasms by stressing the presence in the former of subepithelial dense, cellular stroma resembling that of the ovary, identifying its potential for overt or latent malignancy in 1978. The latest edition of the WHO classification published in 2019 [2] stressed that the distinctive ovarian-type stroma is required for the diagnosis.

MCN is a well-recognized premalignant tumor of the pancreas [3]. Completely resected MCNs with no pathologic evidence of invasive carcinoma have an excellent prognosis, and patients recover after surgery with no relapse [4–6]. Previous data showed that 4.4–16.1% [4,5,7–11] of MCN progressed to invasive carcinoma, which is designated as ‘MCN with associated invasive carcinoma (MCN-AIC)’ according to the latest WHO classification [2]. Microscopically, the invasive component usually resembles conventional pancreatic ductal adenocarcinoma (PDAC), but the prognosis of MCN-AIC is much better than other types of PDAC [12], with reported 5-year survival rate ranging from 26 to 75% [5,6,11,13,14].

At present, the stage assessment of MCN-AIC is recommended to follow conventional staging protocols for pancreatic tumors [2,15,16]. The relationship between the invasive component and the tumor wall (or capsule) is not a recognized histologic prognostic parameter. Previous studies have shown that the pattern of invasion has potential prognostic value for MCN-AICs [5,14,17,18], but the definitions of infiltrative pattern employed in these studies were diverse and the role of these findings in guiding the management of MCN-AIC remains unclear.

In this study, we included 165 cases of MCN with 15 being MCN-AIC. Tumor wall (or capsule) involvement was specifically evaluated. As a result, MCN-AICs with neoplastic invasion not beyond the outer layer of the wall (which we termed encapsulated MCN-AICs) had the same disease-free survival as noninvasive MCNs despite the varying sizes of their invasive component, even for T2 carcinomas. Our observation suggests that encapsulated MCN-AICs are generally less aggressive than those with extracapsular invasion. Different patterns of invasion of MCN-AICs should be separated when evaluated pathologically. With an estimated low risk of recurrence and metastasis, pathologic stage T1 and T2 encapsulated MCN-AIC patients can expect to achieve long-term disease-free survival after complete surgical removal of the tumor with or without adjuvant chemotherapy.

## Materials and methods

### Case selection and histologic analysis

A total of 165 patients who had undergone surgical resection with a final pathologic diagnosis of pancreatic MCN were identified from the pathology database at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, between 1 January 2008 and 31 October 2018.

Clinical information including patient age, sex, date of diagnosis, symptoms, history of pancreatic disease and other conditions, blood serum tumor markers, tumor site, and type of surgery was gathered through medical records review. Radiologic examination results were retrieved from the database and reviewed by an experienced radiologist. For each identified case, information regarding the size of cyst (tumor) and total number of submitted blocks was also obtained from the surgical pathologic reports.

All cases underwent careful gross examination according to our institutional protocol. All available hematoxylin and eosin-stained slides were re-examined and the diagnoses were confirmed by two expert

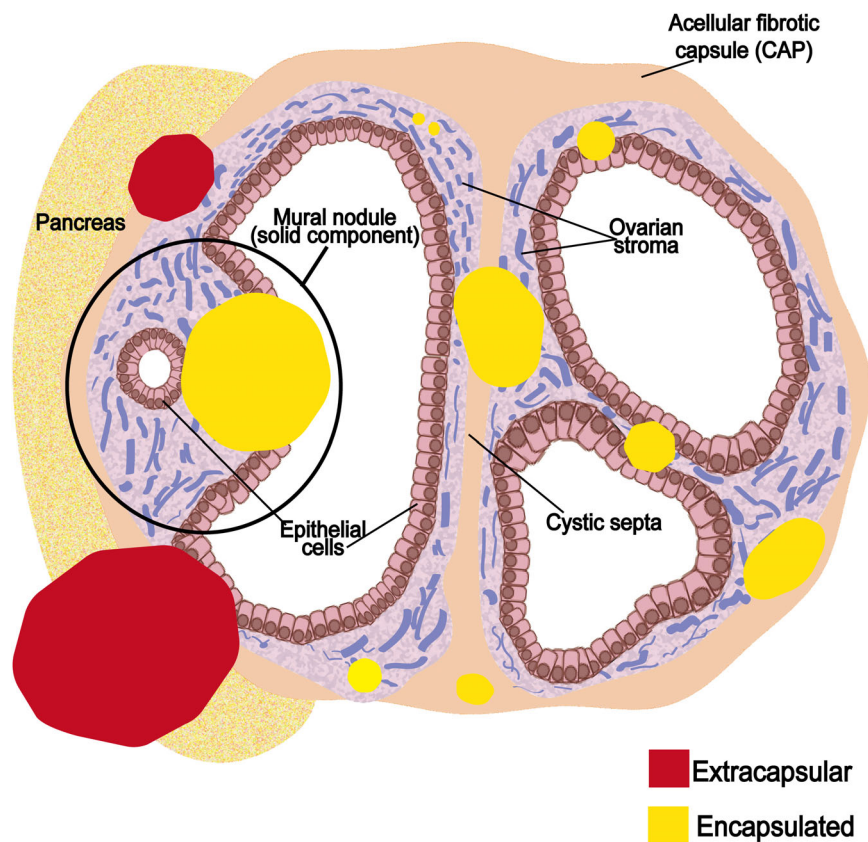
pathologists (YG and CW). Standard criteria [2] were employed for the diagnosis of an MCN, in which the presence of ovarian-type stroma was mandatory. When typical ovarian-type stroma was not evident as a possible result of fibrosis, immunohistochemistry for progesterone receptor, estrogen receptor, and inhibin was performed to ensure correct diagnosis [19]. MCNs without invasive carcinoma were categorized into low-grade dysplasia (LGD) or high-grade dysplasia (HGD) based on the 2019 WHO classification [2]. Based on the size of the largest diameter of invasive component, MCN-AICs were further stratified into MCN with T1a ( $\leq 0.5$  cm invasion), T1b ( $>0.5$  and  $<1.0$  cm invasion), T1c (1.0–2.0 cm invasion), T2 (2.0–4.0 cm invasion), T3 ( $>4.0$  cm invasion), and T4 (celiac axis, superior mesenteric artery, and/or common hepatic artery invasion) carcinoma based on the WHO pTNM pathologic classification and American Joint Committee on Cancer (AJCC) cancer stage, eighth edition [2,16]. Lymphovascular and perineural invasion as well as condition of metastasis were examined. pTNM stage was evaluated for each case. In addition, based on the depth of infiltration, we divided MCN-AICs into two groups: (1) encapsulated MCN-AIC, if neoplastic invasion did not go beyond the outer layer of the wall (confined to ovarian-type stroma, cystic septa, and capsule) and (2) extracapsular MCN-AIC, if the invasive component extended into the surrounding pancreatic and extra-pancreatic tissue (Figure 1). This study was approved by Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine.

### Patient outcomes

Follow-up data including postsurgery treatment, recurrence, metastasis, and overall survival were obtained through medical records searching and phone interviews with patients and/or their families. Patient informed consent was obtained through consent form signature. Survival was measured from the time of surgery to the last time of follow-up.

### Statistical analysis

Categorical variables were compared using  $\chi^2$  test, and Fisher's exact test when cell counts were  $<5$ . Normally distributed continuous variables were compared using a two-sample Student's *t*-test; the Mann–Whitney *U*-test was applied for non-normally distributed variables. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS statistics 23.0; SPSS Inc., Chicago, IL, USA). Survival analysis was performed using the Kaplan–Meier method and then



**Figure 1.** Diagram illustrating the classification of invasion patterns. Measured by the depth of cyst involvement, MCN-AICs are grouped into ‘encapsulated’ and ‘extracapsular’. Note that focal invasion of the fibrous wall without reaching the outer layer of the capsule is considered as encapsulated.

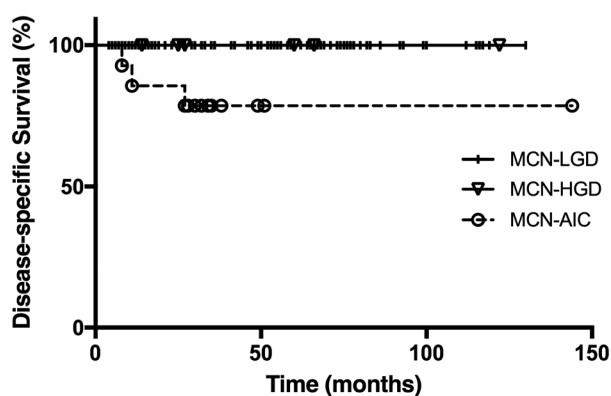
compared using the log-rank test. Kaplan–Meier curves were created with GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA). A *P* value of <0.05 was considered statistically significant.

## Results

A total of 165 MCN patients were identified and included in our study; their clinicopathologic characteristics are listed in Table 1. Our findings confirm that MCNs occur almost exclusively in middle-aged women (93.9% female, mean age = 47.3 years) with tumor mostly located in the pancreatic body and tail. The prevalence of associated invasive carcinoma (9.1%) is slightly less than the summarized data of 15% from the latest WHO classification [2]. In comparison with non-invasive MCNs, MCN-AIC patients were older in age ( $p = 0.003$ ) with a tumor of larger

**Table 1.** Clinicopathologic characteristics of 165 MCNs.

Total number registered	165
Age, years (range)	47.3 ± 15.5 (18–89)
Sex ratio, female:male % (n)	93.9% (155):6.1% (10)
Presence of symptoms % (n)	48.2% (79/164)
Elevated serum CA19-9 level % (n)	21.2% (22/104)
Tumor size, cm (range)	5.5 ± 3.5 (1.0–18.0)
Tumor location (head/body or tail), % (n)	16.1% (10):93.9% (155)
History of pancreatic disease % (n)	16.0% (26/163)
Diabetes	6.1% (10)
Pancreatitis	8.6% (14)
Pancreatic cyst	1.2% (2)
Type of surgery % (n)	
Pancreatoduodenectomy	5.5% (9)
Distal pancreatectomy	87.3% (144)
Middle segment pancreatectomy	2.4% (4)
Enucleation	4.2% (7)
Omentectomy	0.6% (1)
Histopathologic grading % (n)	
LGD	86.7% (143)
HGD	4.2% (7)
Associated invasive carcinoma	9.1% (15)



**Figure 2.** Survival comparison of MCN-LGD, MCN-HGD, and MCN-AICs ( $p < 0.0001$ , log-rank test). The 5-year disease-specific survival rate of noninvasive MCNs and MCN-AICs is 100 and 78.6%, respectively.

size ( $p < 0.001$ ). The presence of symptoms and raised carbohydrate antigen (CA) 19-9 were not common in noninvasive MCNs but appeared more frequent in MCN-AICs ( $p = 0.038$  and  $0.035$ , respectively). No further treatment was given to patients without invasive carcinoma in this study. As shown in Figure 2, the prognosis of MCNs without invasion was good: during a mean follow-up period of 44.4 and 52.3 months, respectively, MCN patients with either LGD or HGD had a 5-year survival of 100%. Twenty-two patients lacked outcome information and one patient died of brain hemorrhage; these were excluded from the survival analysis. MCN-AIC patients had worse outcome. In a mean follow-up period of 40.6 months, the 5-year disease-specific survival of the MCN-AIC patients was 78.6% (14 with accessible follow-up data and 1 patient lacked outcome information).

The clinicopathologic features of 15 MCN-AICs are listed in Table 2. The patients were exclusively female. The average age at the time of surgery was  $51.2 \pm 11.5$  (range: 27–68) years. Tumors were all located in the body and tail. The average diameter of the cysts was 8.4 cm (range: 2.0–17.0, median: 7). Ten of 15 (66.7%) were symptomatic. Three (20%) suffered diabetes prior to tumor detection. Elevated blood serum CA19-9 was detected in 5 of the 12 patients where this was known. Radiologically, mural nodules or a solid component were observed in nine cases, with a mean size of 1.8 cm. Computed tomography scan imaging showed different degrees of enhancement in these areas (Figure 3). One patient (case 15) had suspected colon involvement on presurgery imaging; this was later confirmed by

pathology. No patient had evidence of distant metastasis prior to surgery.

All 15 cases underwent careful gross examination. The capsule and surrounding tissues were partially or entirely submitted, with a mean number of blocks of 17.8 (range: 5–37, median: 16) per tumor. The mean number of sections submitted per 1 cm of the greatest dimension of the MCN was 1.85 (range: 1.46–3.25, median: 2.17).

Measured by the size of the invasive component and based on the AJCC cancer stage system, seven cases were pathologically classified as T1a, three cases as T1c, four cases as T2, and one case as T4. No T1b patient was identified in our database. All 15 cases had regional lymph nodes submitted; no lymphovascular invasion was observed. In all submitted samples, no perineural invasion was found. Distant metastasis at the time of surgery was not detected. Accordingly, 10 cases were staged as IA, 3 cases as IB, and 1 case as III. Based on our definition, 12 of 15 MCN-AICs were classified as encapsulated. Among them, 11 contained varying sizes of invasive component into the ovarian-type stroma and/or septa; the cyst wall was not infiltrated (Figure 4A,B). Another encapsulated case had multifocal invasion of ovarian-type stroma and one focus of invasive carcinoma (0.3 cm) in the capsule while the outer layer of the capsule was not penetrated (Figure 4C). The other three cases had extracapsular invasion (Figure 4D–F): case 13 had unifocal carcinoma with extensive invasion. In case 14, there were multifocal invasive carcinomas which extended through the capsule and infiltrated pancreatic parenchyma and surrounding tissues. Case 15 presented diffuse extrapancreatic invasion including colon and the superior mesenteric artery.

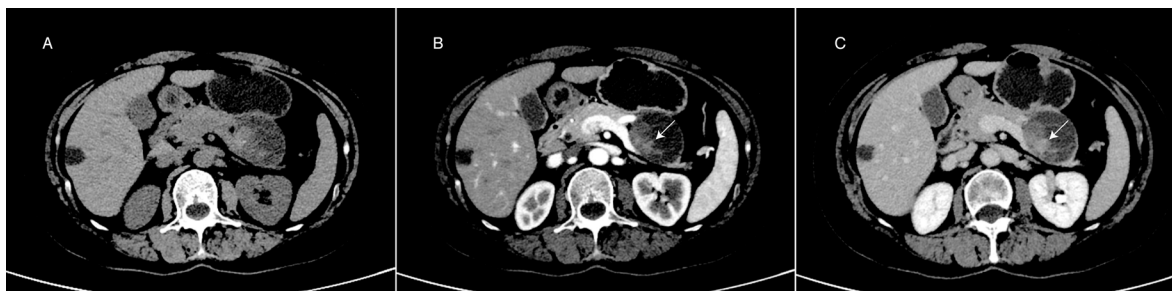
Invasive components in most (80%) cases were moderately differentiated PDAC. Case 10 was confirmed as undifferentiated carcinoma with osteoclast-like giant cells, case 13 as moderately differentiated adenosquamous carcinoma, and case 14 as PDAC with a focal signet ring cell component (Figure 5). In 14 MCN-AICs, HGD was observed in the adjacent epithelia while 1 T1a MCN-AIC only showed LGD.

No patients received neoadjuvant chemotherapy. Five patients with more advanced disease received postoperative chemotherapy. In terms of cancer stage, survival was not significantly different between the 'stage IA' and 'stage IB' groups ( $p = 0.2579$ ) (Figure 6A). When their clinical courses were compared with the extent of invasion, the difference was statistically significant ( $p < 0.0001$ ) (Figure 6B): survival of encapsulated cases was excellent, with 11 of

Table 2. Characteristics of 15 patients with MCN-AIC.

Patient	Age	Gender	Symptoms	Elevated CA19-9	Tumor size (cm)	Pattern of invasion	Largest dimension of invasion (cm)	pTNM classification	Prognostic stage group	Histology of invasive component	Chemotherapy	Follow-up period (months)	Clinical course	Blocks submitted	Blocks submitted per 1 cm of the greatest dimension of the MCN
1	51	F	Abdominal pain	Not known	4	Encapsulated	<0.1	T1a, NO, MO	IA	Ductal adenocarcinoma	No	144	AAW	6	1.5
2	62	F	Abdominal discomfort	No	2	Encapsulated	<0.2	T1a, NO, MO	IA	Ductal adenocarcinoma	No	49	AAW	5	2.5
3	50	F	Abdominal pain	Yes	14	Encapsulated	3	T2, NO, MO	IB	Ductal adenocarcinoma	Yes	38	AAW	27	1.93
4	53	F	Back pain	No	17	Encapsulated	<0.1	T1a, NO, MO	IA	Ductal adenocarcinoma	No	35	AAW	37	2.18
5	31	F	Abdominal pain	No	6	Encapsulated	2.5	T2, NO, MO	IB	Ductal adenocarcinoma	Yes	34	AAW	14	2.33
6	56	F	No	Yes	4	Encapsulated	<0.2	T1a, NO, MO	IA	Ductal adenocarcinoma	No	30	AAW	13	3.25
7	52	F	No	No	10	Encapsulated	2	T1c, NO, MO	IA	Ductal adenocarcinoma	Yes	32	AAW	21	2.1
8	68	F	No	No	13	Encapsulated	2	T1c, NO, MO	IA	Ductal adenocarcinoma	Yes	28	AAW	19	1.46
9	54	F	No	Yes	7	Encapsulated	<0.2	T1a, NO, MO	IA	Ductal adenocarcinoma	No	50	AAW	15	2.14
10	57	F	Abdominal pain	Not known	8	Encapsulated	4	T2, NO, MO	IB	Undifferentiated carcinoma with osteoclast-like giant cells	Not known	—	Not known	16	2
11	50	F	Abdominal pain	Yes	6	Encapsulated	<0.1	T1a, NO, MO	IA	Ductal adenocarcinoma	No	51	AAW	15	2.5
12	27	F	Abdominal pain	No	5	Encapsulated	<0.1	T1a, NO, MO	IA	Ductal adenocarcinoma	No	28	AAW	12	2.4
13	66	F	No	Yes	12	Extracapsular	3	T2, NO, MO	IB	Adenosquamous carcinoma	No	8	DOD	26	2.17
14	38	F	Abdominal pain	Yes	6.5	Extracapsular	1.7	T1c, NO, MO	IA	Ductal adenocarcinoma with focal signet ring cell component	No	11	DOD	18	2.77
15	53	F	Abdominal pain	Not known	11	Extracapsular	Extensive	T4, NO, MO	III	Ductal adenocarcinoma	Yes	27	DOD	23	2.1

AAW, alive and well; DOD, died of disease; F, female.



**Figure 3.** Preoperative computed tomography (CT) images of case 6: a 56-year-old female who was found to have a cystic lesion in her pancreas during her regular medical examination. Abdominal CT scan shows a cystic lesion with septa, nodules, and solid components in the pancreatic body and tail. The nodules and solid components are slightly hyperdense in the precontrast image (A), and enhance slowly and moderately in the postcontrast images in the arterial (B, arrow) and venous (C, arrow) phases.

12 patients (one case lacked follow-up information) alive without any recurrence or metastasis, even with a pT classification of T2, leading to a 5-year disease-specific survival of 100%. In contrast, all three patients with extracapsular MCN-AIC had limited survival. One of them received chemotherapy but died 27 months later from gastric metastasis. The other two patients recurred shortly after surgery and died within 8 and 11 months, respectively.

## Discussion

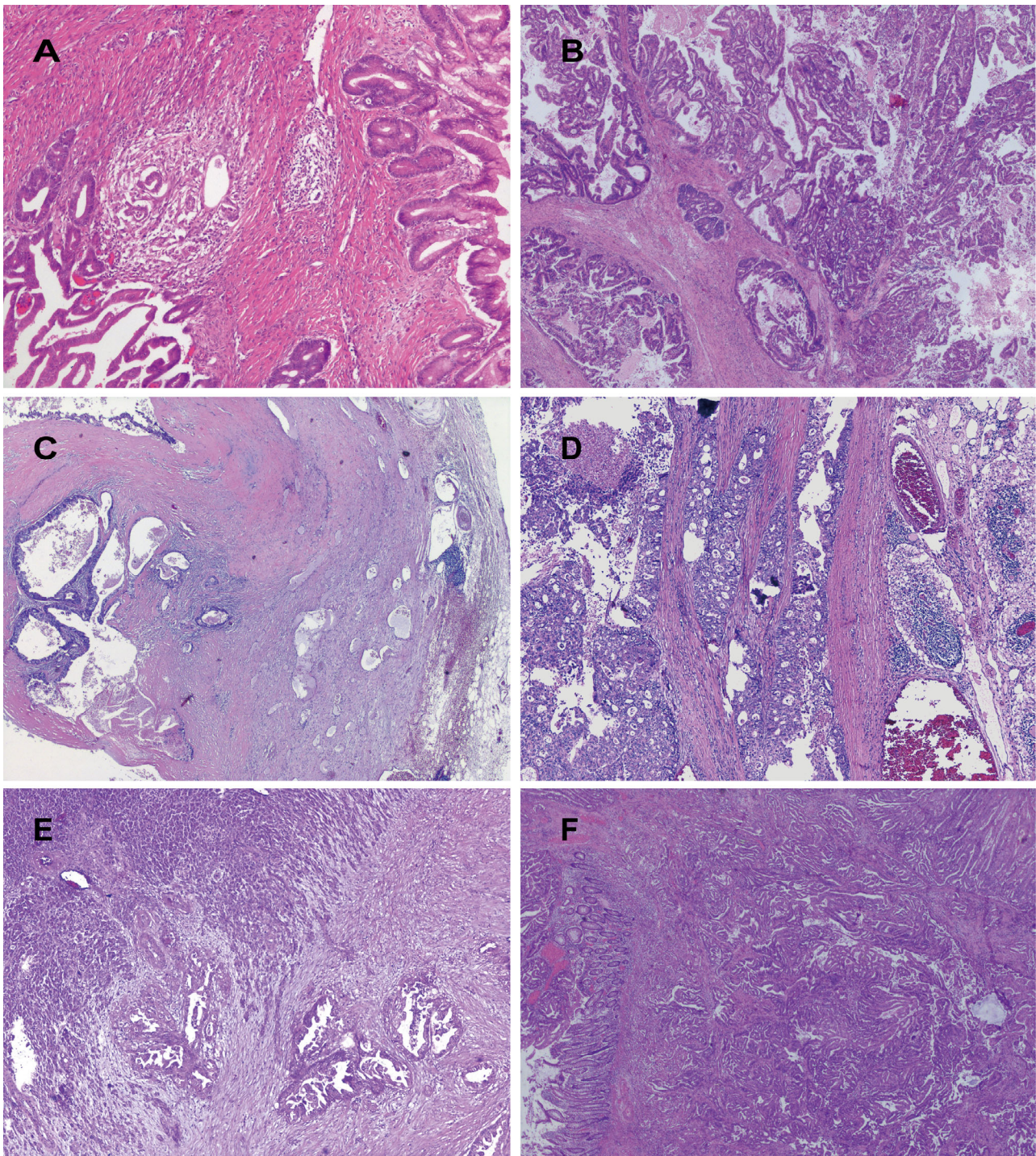
This study describes the clinicopathologic characteristics of 165 MCNs. In accordance with previous studies, MCNs with LGD/HGD had no recurrence or disease-related death. This confirms that noninvasive MCNs are curable with complete surgical resection.

Fourteen MCN-AIC cases had a 5-year disease-specific survival rate of 78.6%, superior to an approximately 60% 5-year survival summarized in a previous systematic review [6]. Based on the subgroup, encapsulated MCN-AICs, even with a pT classification of T2, had the same favorable prognosis as that of MCNs without invasion. Conversely, patients with extracapsular MCN-AIC had limited survival periods. These two very different clinical courses suggest that encapsulated and extracapsular MCN-AICs may be evaluated separately during pathologic examination.

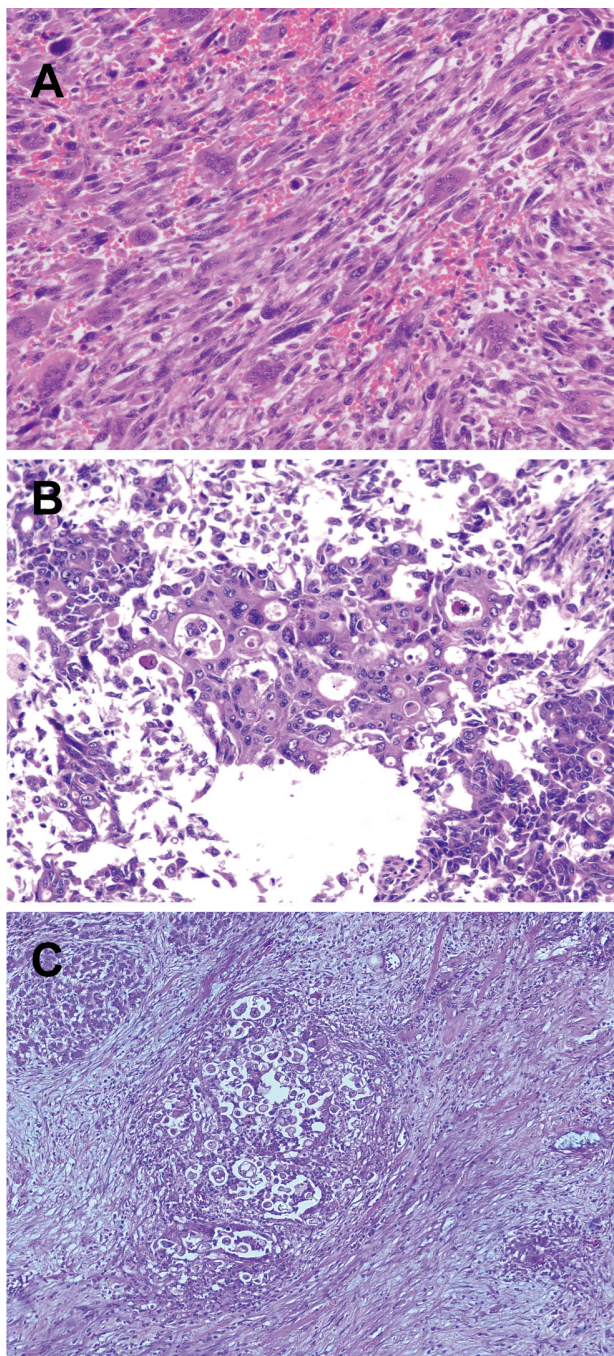
MCN-AIC is now assessed following the protocols used for PDAC [2,15,16]. The relationship of invasion to the tumor capsule is not listed as an evaluation factor in the current classifications or the guidelines for MCN-AICs, but there are data on its possible prognostic value from older studies. Zamboni *et al* [17] first concluded in 1999 that the depth of invasion (tumor wall and

peritumoral) was an independent prognostic factor for mucinous cystic tumor as all three ‘intratumoral’ types of invasive mucinous cystadenocarcinoma (MCC) in their research were associated with survival. In contrast, three of five invasive MCCs with invasion ‘confined to the tumoral wall’ and six of eight with ‘peritumoral’ type of invasion died of the disease. Similarly, in Crippa *et al*’s [5] observation, only 3 of 14 (21.4%) MCNs with intracapsular invasion died of pancreatic cancer, while 4 of 5 (80%) MCNs with extracapsular invasion experienced tumor recurrence and eventually died of disease. In 2013, the terminology ‘minimally invasive’ was used in Lewis *et al*’s study to refer to a limited degree of invasion confined to the ovarian-type stroma and the authors concluded that this suggested good prognosis [18]. In the above-mentioned studies, however, detailed information on the size of the invasive component or their pTNM classification was not given. More recently, two studies [4,20] provided evidence that T1a/T1b MCN-AIC, which was limited to the ovarian-type stroma, cystic septa, or hyalinized stroma in the superficial layer of the cyst wall, had excellent survival similar to noninvasive MCN. These four cases were all at relatively early stages of invasion with invasive foci measuring up to 0.7 cm

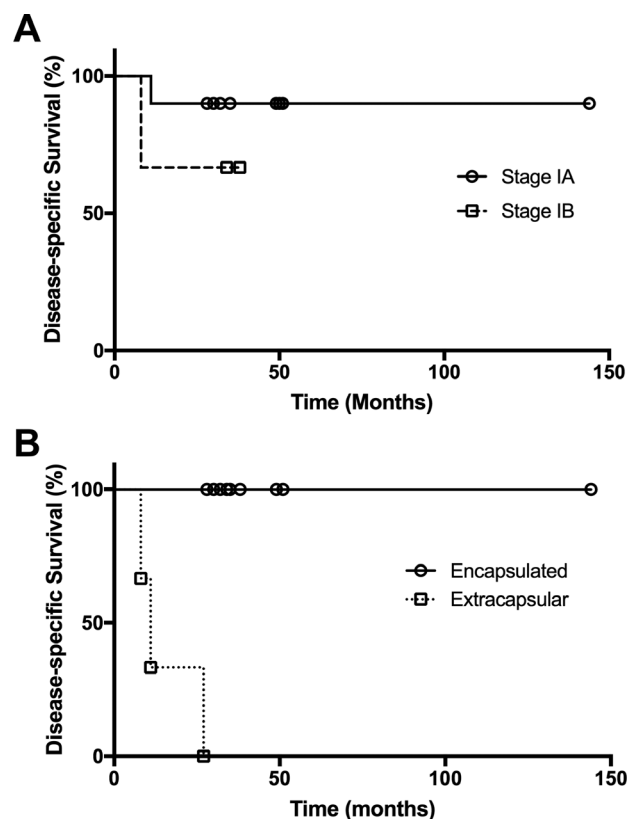
To the best of our knowledge, we have presented here, for the first time, two cases of T1c and two cases of T2 MCN-AIC with encapsulated invasion. Notably, one T1c encapsulated MCN-AIC (case 8) had an invasive focus embedded in the capsule’s acellular collagen stroma. All four T1c/T2 encapsulated MCN-AIC patients are disease-free after surgery. For pancreatic cancer, the eighth AJCC staging system stages T1 and T2 carcinoma without lymph node invasion and distant metastasis separately as IA and IB [16]. Large cohort studies have shown that stage I PDAC patients’ survival rates drop from stage IA to IB; the reported 5-year survival rate for stage IA PDAC ranges from



**Figure 4.** Representative micrographs of MCN-AICs showing invasion of varying sizes and depths. (A) A carcinoma focus located within ovarian-type stroma and minimal in size (less than 0.1 cm) (case 1). (B) Extensive invasion with the greatest dimension of 3 cm (case 3). Although large in size, the invasive component was restricted to ovarian-type stroma and cyst septa. (C) A 0.3 cm carcinoma focus embedded in the superficial acellular hyalinized capsular stroma, while the outer layer of the cyst remains clear (case 8). (D) Invasive component infiltrating throughout the whole cyst wall (case 13), presumably arising from the mural nodule (left) and spreading into the fibrotic capsule (central) with no perineural and vascular involvement (right). (E) Invasive carcinoma intruding into the surrounding pancreatic parenchyma (case 14). (F) Extensive invasion with carcinoma penetrating through the intestinal wall to the epithelial surface (case 15). Hematoxylin and eosin stain.



**Figure 5.** Representative micrographs of rare histologic variants of ductal adenocarcinoma in MCN-AIC. (A) A component with prominent infiltration by histocytes and osteoclast-like giant cells (case 10). The case was diagnosed as undifferentiated carcinoma with osteoclast-like giant cells. (B) An invasive component showing neoplastic cells presenting squamous differentiation (case 13). The case was diagnosed as moderately differentiated adenosquamous carcinoma. (C) In this case, the atypical epithelial cells contained intracytoplasmic mucin that displaced the nuclei toward the periphery, resembling signet ring cells which are more typically seen in gastric carcinoma (case 14). The case was diagnosed as PDAC with a focal signet ring cell component. Hematoxylin and eosin stain.



**Figure 6.** (A) Survival comparison of stage I MCN-AICs with different substages (stage IA versus stage IB) ( $p = 0.2579$ ). (B) Survival comparison of MCN-AICs with different patterns of invasion (encapsulated versus extracapsular) ( $p < 0.005$ , log-rank test).

30.6 to 83.7% [21,22], and stage IB PDACs have a lower overall survival than stage IA [23–26]. By contrast with stage I PDACs, 11 encapsulated MCN-AICs cases with 9 stage IA and 2 stage IB in this study showed no differences in survival: all patients remained free of disease after a mean follow-up period of 40.6 months. This suggests that encapsulated MCN-AICs generally have a benign clinical course irrespective of the size and depth of invasion. Hypothetically, a hyalinized capsule can serve as a barrier against neoplastic cell migration: carcinoma restricted to the ovarian-type stroma and septa represents an early stage of cancer progression, while carcinoma invading the hyalinized capsule indicates a greater degree of neoplastic expansion. Nonetheless, as long as the outer layer of the capsule is not breached, tumor invasion can still be perceived as restricted. As the status of capsular invasion more accurately predicted patients' clinical outcomes than AJCC cancer stage in our study, it may be superior in estimating survival for



MCN-AICs. We propose that MCN-AICs with different invasion patterns are described specifically in pathologic reporting, considering that this 'extent of invasion'-based categorization can be a possible supplement/reference to the widely used staging system. As our observations were made from a limited number of cases, more supporting evidence is welcomed. Moreover, this observation along with other studies on MCNs again highlight the importance of ample sampling of MCNs in pathologic examination, to avoid missing any extensive invasion.

Another focus of this study is how much benefit adjuvant chemotherapy may bring to MCN-AIC patients. An international consensus has been reached that all patients with resected pancreatic cancer who did not receive preoperative therapy should be offered adjuvant chemotherapy in the absence of contraindications [27–29]. The role of systemic chemotherapy in treating MCN-AIC remains less discussed. The current recommendation is that MCN-AIC patients follow the standardized chemotherapy-based management applied in treating conventional pancreatic cancer [30,31]. Recently, a retrospective analysis suggested that, for early-stage PDAC patients with carcinoma measuring <1 cm (T1a/T1b), survival is not significantly different between patients who received adjuvant treatment and those who did not [32]. As for MCN-AICs, Hui *et al* [4] presented three well-documented T1a/T1b MCN-AICs with favorable prognosis and advocated for regular follow-up to reduce the use of systemic chemotherapy. A case report from Japan also showed a T1a MCN-AIC patient who recovered without chemotherapy (the patient ceased chemotherapy after experiencing significant adverse reactions) [20]. All these four cases had invasion limited to ovarian-type stroma, cyst septa, or the cyst capsule which might be identified as 'encapsulated' by our definition. In this study, we witnessed that seven T1a MCN-AICs with encapsulated invasion recovered without adjuvant therapy. This new evidence is in accordance with the previous four cases showing that T1a/T1b encapsulated MCN-AICs have the same survival as that of noninvasive MCN; this suggests that these tumors can be cured by surgery, and close follow-up rather than systemic chemotherapy is strongly recommended.

To date, there are scarce data on the contribution of chemotherapy in treating T1c/T2 MCN-AIC cases. In our study, the treatment of four patients with T1c/T2 encapsulated MCN-AICs had followed guidelines and they received postoperative chemotherapy. At the last follow-up, the patients were all alive and well. Following our previous hypothesis, as the cyst capsule comprised

dense acellular collagen and was not extensively penetrated by neoplastic cells, the malignancies were in effect localized. For these patients, the risk of relapse or metastasis after resection is potentially low. Complete recovery can be expected with timely surgery and adjuvant chemotherapy. It is worth noting that we have only presented a small number of cases in this category, and none of the MCN-AICs had lymphovascular invasion and perineural invasion. More cases with relevant data are wanted to support our opinion.

To conclude, encapsulated and extracapsular MCN-AICs should be differentiated during pathologic evaluation, as encapsulated MCN-AICs had a favorable disease-free survival similar to that of non-invasive MCNs. We propose that the pattern of invasion is added as a new histologic parameter for pathologic examination and diagnosis, given that it may become a prognostic factor. Alongside the classic T stage classifications, evaluating invasion pattern of MCN-AICs may further help optimize the choice of patient management. For surgically resected T1 and T2 encapsulated MCN-AICs, where specimens have been entirely submitted and adequately sampled, with negative resection margins during pathologic examination, patients can achieve long-term recovery with adjuvant chemotherapy and close follow-up. Given the limited number of cases and the study design's retrospective nature, future studies with more prospective data are needed to support this proposal.

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## Author contributions statement

HL and YG conceived the study design. HL, WX and XL carried out data collection, generation of figures, and data analysis. TW, JX, CW, S-YX and YG interpreted data. HL searched the literature and wrote the draft manuscript. S-YX and YG revised the manuscript. All authors had final approval of the submitted and published versions.

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