



Mucinous cystic neoplasms of the pancreas in the modern era. Experience with 707 patients



Maria Ahmad, Felipe B. Maegawa, Elizabeth De La Rosa, Brian Davis, Alan Tyroch, Ioannis T. Konstantinidis*

Department of Surgery, Texas Tech University Health Sciences Center, El Paso, TX, USA

ARTICLE INFO

Article history:

Received 31 March 2020
Received in revised form
23 May 2020
Accepted 3 September 2020

Presented at: Oral Presentation, SWSC 2020 Annual Meeting

Keywords:

Mucinous cystic neoplasms
Pancreas
Invasive disease
NCDB
Treatment outcomes

ABSTRACT

Background: Mucinous Cystic Neoplasms are mucin producing cysts of the pancreas with malignant potential. The existing literature on treatment outcomes is limited to relatively small surgical series.

Methods: We reviewed the National Cancer Database assessing the outcomes of patients with mucinous cystic neoplasms between 2004 and 2016. Kaplan-Meier method and log rank test were used to make survival comparisons.

Results: A total of 707 patients were identified; 492(69.6%) underwent pancreatectomies. The majority of patients were women (71.4%), with median age 65 years (range: 22–90). Most common operation was partial pancreatectomy ie distal (48.4%) whereas 21.7% underwent a Whipple. Patients who were not operated were more frequently stage IV (40%) whereas patients who were operated had more frequently invasive adenocarcinoma (74.8%). Patients who underwent pancreatectomy had better survival compared to these who didn't undergo surgery (81.4 vs 6.6 months; $p < 0.001$). Comparing patients who underwent pancreatectomy and had invasive disease versus patients who had in situ disease the former were older (median age 62 vs 55.5 years $p = 0.004$) and more frequently men (26.1 vs 16.1%; $p = 0.03$), however they had similar tumor size (5.5 vs 7 cm respectively; $p = 0.14$) and similar tumor differentiation (moderately differentiated 50% vs 38.1%; $p = 0.49$). Patients with non-invasive (in situ) disease had prolonged survival compared to these with invasive disease (median OS not reached vs 50.2months; $p < 0.001$). After Cox proportional hazard regression nodal positive disease was the most important factor of decreased survival for invasive adenocarcinoma (HR: 2.2; $p < 0.001$).

Conclusion: Patients with adenocarcinoma arising from a mucinous cystic neoplasm of the pancreas have excellent survival when they undergo pancreatectomy especially if the disease is still in situ. However, 3/4 of patients who undergo resection have already developed invasive adenocarcinoma and nodal status dominates their prognosis. Advanced age but not the size of the cyst correlate with the presence of invasive disease.

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Introduction

Pancreatic mucinous cystic neoplasms (MCNs) are mucin producing pancreatic cysts with malignant potential, occurring typically in peri-menopausal women. Their incidence in surgical series of resected pancreatic cysts varies between 10 and 45%.^{1–3}

Most of the guidelines on the management of pancreatic cystic lesions recommend resection for MCNs due to their malignant potential.^{4–6} The European guidelines recommend a more selective approach and recommend resection for lesions that are ≥ 4 cm, are

symptomatic or have radiologic risk factors.⁷ The existing surgical series reporting treatment outcomes for MCNs have identified factors associated with malignancy (size ≥ 6 cm, presence of nodules, duct dilation, male, pancreatic head and neck location).^{8,9} However, these studies are coming from tertiary centers, are relatively small and do not reflect the nationwide management of these tumors.

In an effort to overcome the above limitations, we examined the National Cancer Database, as it captures approximately 70% of new cancer patients treated nationwide with detailed clinicopathologic and treatment data.¹⁰ Furthermore, it separates cases of in situ adenocarcinoma or invasive adenocarcinoma. The aims of the present study were to determine nationwide outcomes in the treatment of MCNs, to compare patients with in situ vs invasive

* Corresponding author. 2000B Transmountain Road, El Paso, TX, 79911, USA.
E-mail address: ioannis.konstantinidis@ttuhsc.edu (I.T. Konstantinidis).

adenocarcinoma and identify factors associated with survival for invasive disease.

Materials and methods

The National Cancer Database (NCDB) is a hospital-based cancer registry sponsored by a joint program between the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society. It captures data from more than 1500 hospitals.¹⁰

For the purpose of this study we used the Participant Use Data Files (PUF) for Pancreas which are Health Insurance Portability and Accountability Act (HIPAA)-compliant data files containing de-identified data. We reviewed patient data of patients 18 years or

older, from 2004 to 2016, with the histologically confirmed diagnosis of mucinous cystic neoplasms. Only patients with the histologic code of 8470 (mucinous cystadenocarcinoma) were included (International Classification of Diseases for Oncology, 3rd edition (ICD-O-3)) and we excluded all other codes including mucinous adenocarcinoma and papillary mucinous adenocarcinoma to prevent contamination from pancreatic ductal adenocarcinoma and intraductal papillary mucinous adenocarcinoma patients.

Patient demographics including age, gender, race, insurance status, operative data such as type of surgery, pathology data such as tumor size and differentiation. Postoperative outcomes examined included length of stay, readmission within 30 days, mortality at 30-days, and 90-days. Long term outcome was examined with overall survival. Patient comorbidity was expressed with the Charlson Comorbidity Index (CCI). With regards to the surgical margins we used the following definitions: R0: margins are microscopically negative, R1: microscopic residual tumor, R2: macroscopic residual tumor. Cases coded as: residual tumor no otherwise specified or margins not evaluable were treated as unknown. With regards to the behavior of the tumor. Benign tumors or tumors of uncertain behavior are not reported to the NCDB. All the tumors included in this study had an NCDB code of Carcinoma In Situ (confined to epithelium) or Invasive (invasive adenocarcinoma). With regards to tumor size this variable describes the most accurate measurement of a solid primary tumor, usually measured on the surgical resection specimen.

Statistical analysis

Continuous variables are presented as median and range. Categorical variables are presented as proportions. Group differences were assessed using Fisher exact or Pearson χ^2 test for categorical variables. Continuous variables were compared with the student's *t*-test when the distribution was normal, or the Wilcoxon rank-sum test and Kruskal-Wallis test when the distribution was not normal.

Survival curves were constructed with the Kaplan-Meier method and differences assessed with the log rank test. Cox proportional hazard regression model was used as appropriate. Statistical analysis was performed using SPSS Statistics v23 software (IBM Corp., Armonk, NY).

Results

1 Clinicopathologic characteristics

During the period 2004–2016, we identified 707 patients with the diagnosis of Mucinous Cystic Adenocarcinoma, 492 (69.6%) underwent pancreatectomy and represent the focus of this study. The majority of these patients were women (76.4%) and white (83.3%) with a median age of 60 years and a Charlson comorbidity index of 0 for 67.1%. Table 1 illustrates the clinicopathologic data of the surgical cohort.

Most common pancreatectomies were partial pancreatectomies (ie distal, 48.4%) and Whipples (21.7%). Surgical margins were negative in 93.4%. Lymph nodes were evaluated in 431 patients (88%) and were positive in 15.8%. Lymph node positivity for resected invasive adenocarcinomas was 18.5%. The majority of tumors were moderately differentiated (49%).

Median length of hospital stay was 7 days; 30-day readmission and mortality rates were 6.8% and 2.9% respectively, whereas 90-day mortality rate was 6.5%.

2 Mucinous Cystadenocarcinomas. In Situ versus Invasive

Table 2 illustrates a comparison between the patients who had

Table 1
Clinicopathologic characteristics of 492 patients who underwent pancreatectomy for Mucinous Cystic Neoplasms of the Pancreas.

Variable	n (%)
Median Age (range), y	60 (22–90)
Female gender	376(76.4)
Race	
White	410 (83.3)
African American	52 (10.6)
Other	30 (6.1)
Insurance status	
Private	241 (49)
Medicare	184 (37.4)
Medicaid	28 (5.7)
Other/Uninsured	39 (7.9)
Charlson-deyo comorbidity index	
0	330(67.1)
1	125(25.4)
2	26(5.3)
≥3	11(2.2)
Histology/behavior	
Invasive	368 (74.8)
In-Situ	124(25.2)
Grade	N = 275
Well differentiated	85 (31)
Moderately differentiated	135(49)
Poorly/un-differentiated	55(20)
Primary site	
Head	112(22.8)
Body	48(9.8)
Tail	243(49.4)
Other	89 (18)
Type of Pancreatectomy	
Partial pancreatectomy (ie distal)	238(48.4)
Pancreaticoduodenectomy (Whipple)	107(21.7)
Total pancreatectomy	32(6.5)
Other	115(23.4)
Surgical Margins	N = 457
R0	427(93.4)
R1	27 (5.9)
R2	3 (0.7)
Regional nodes examined	N = 431
Positive nodes	68 (15.8)
Hospital Type	N = 439
Academic/Research NCI designated	209 (47.6)
Comprehensive community cancer programs	143(32.6)
Integrated network cancer programs	64(14.6)
Community cancer programs	23(5.2)
Hospital Stay, median (range) d	7(0–134)
Readmission within 30 d	N = 470 32(6.8)
30 d mortality	N = 449
	13 (2.9)
90 d mortality	N = 447
	29 (6.5)

Table 2

Comparison of 124 patients with in situ adenocarcinoma versus 368 patients with invasive adenocarcinoma arising from a Mucinous Cystic Neoplasm of the Pancreas.

Factor n(%)	In-Situ n = 124	Invasive n = 368	P value
Median Age (yrs)	55.5	62	0.004
Male Gender	20 (16)	96 (26)	0.03
Charlson-deyo comorbidity index			0.5
0	85(68.5)	245(67)	
1	27(22)	98(27)	
2	9(7)	17(5)	
≥3	3(2)	8(2)	
Median Tumor size (cm)	7	5.5	0.14
Tumor differentiation			0.5
Well differentiated	7(33)	78(31)	
Moderately differentiated	8(38)	127(50)	
Poorly/un-differentiated	6(29)	49(19)	
Type of Pancreatectomy			0.1
Partial pancreatectomy (ie distal)	70(56.5)	168(46)	
Pancreaticoduodenectomy (Whipple)	18(14.5)	89(24)	
Total pancreatectomy Other	9(7)	23(6)	
Readmission within 30 d	9(7)	23(7)	0.8
30 d mortality	1(1)	12(3)	0.3
90 d mortality	1(1)	28(8)	0.02
Median Survival -months	Not reached	50.2	<0.001

in situ (n = 124) versus invasive (n = 368) adenocarcinoma. The invasive group was older (62 vs 55.5 years; $p = 0.004$) and with higher proportion of men (26% vs 16%; $p = 0.03$).

There was no difference in the Charlson comorbidity index, type of operations performed, tumor differentiation, re-admission and 30 day mortality rates. The 90 day mortality rate was elevated in the invasive group (8% vs 1%; $p = 0.02$). Interestingly, tumor size was larger for the in situ group although this didn't reach statistical significance (7 cm vs 5.5 cm; $p = 0.14$). The medial overall survival of patients with non-invasive disease was not reached (median fu = 49.5 months) versus 50.2 months for those with invasive

adenocarcinoma (median fu = 33 months) ($p < 0.001$; Fig. 1).

3 Long term Outcome for Invasive Mucinous Cystadenocarcinomas

Patients who didn't undergo surgery had more frequently stage IV disease (40%) and a median overall survival of 6.6 months, significantly worse compared to patients with invasive disease who underwent resection (50.2 months; $p < 0.001$; 5 year overall survival 35.4%).

Table 3 represents a multivariate logistic regression analysis for

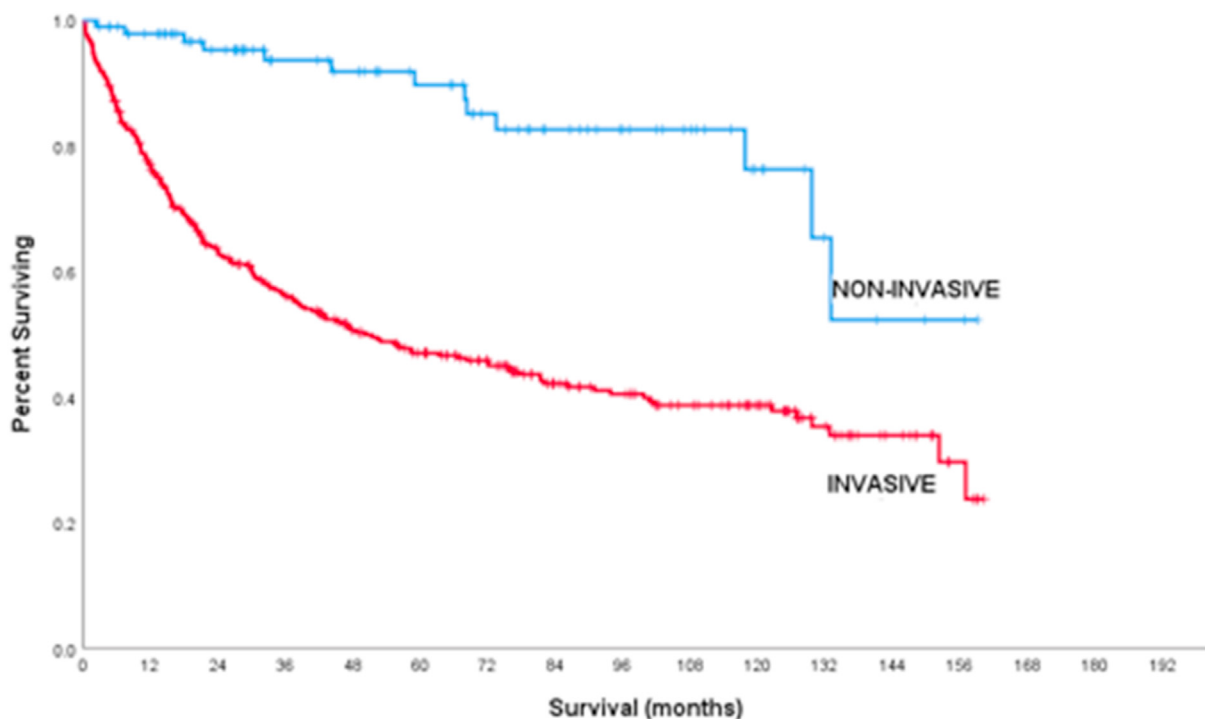


Fig. 1. Survival Outcomes for 492 patients who underwent pancreatectomy for Mucinous Cystic Neoplasms. Patients with non-invasive disease (n = 96) has a significantly improved survival versus patients with invasive disease (n = 356) (Median OS: not reached versus 50.2months; $p < 0.001$).

Table 3

Multivariate Cox Proportional Hazard Regression Model for predictors of overall survival in patients with MCN who underwent pancreatectomy and were found to have invasive adenocarcinoma.

Factor	HR (95% CI)	P value
Age	1.03 (1–1.05)	0.007
Gender		
Male (ref)		
Female	1.32 (0.88–1.98)	0.17
Race		
White (ref)		
African American	1.4(0.7–2.7)	0.3
Other	0.6(0.2–1.9)	0.35
Charlson Comorbidity Index		
0 (ref)		
1	1.2 (0.7–1.8)	0.5
≥2	1.1	0.7
Facility Type		
Academic/Research NCI designated (ref)		
Comprehensive community cancer programs	1.2 (0.8–1.9)	0.4
Integrated network cancer programs	1.6 (0.9–2.8)	0.08
Community cancer programs	0.9 (0.3–2.3)	0.8
Surgical Margin		
R0 (ref)		
R1	1.3 (0.7–2.4)	0.4
Lymph Node positivity		
N0 (ref)		
N1	2.2 (1.5–3.3)	<0.001
Tumor differentiation		
Well differentiated (ref)		
Moderately differentiated	1.2 (0.8–1.9)	0.4
Poorly/un-differentiated	1.3 (0.8–2.3)	0.3

overall survival for patients with invasive adenocarcinoma. The most powerful predictor for survival was the status of the regional lymph nodes. The median OS for patients with nodal positive disease was significantly worse compared to patients with nodal

negative disease (16 months (median fu = 16months) vs 81.4months (median fu = 43 months); $p < 0.001$; Fig. 2).

Discussion

Mucinous cystic neoplasms (MCNs) of the pancreas are relatively rare. Due to their malignant potential surgical resection is recommended in appropriate candidates.^{4,5} In this contemporary large series utilizing the National Cancer Database and reflecting nationwide outcomes on patients with in situ or invasive adenocarcinoma, patients with non-invasive disease had an excellent outcome with median overall survival not reached whereas patients with invasive cancer had a 5Y survival of 35.4%. Interestingly, the pathologic size between in situ and invasive disease was not different with even large tumors could have only in situ disease. Patients with invasive disease were 6.5 years older and more frequently men compared to patients with in situ disease. The most powerful prognostic factor for invasive adenocarcinoma was the lymph node status.

The existing series on MCNs are relatively small. In one of the largest earlier reports combining the experience of Massachusetts General Hospital and University of Verona with 163 resected patients factors associated with malignancy were older age and a cyst size 6 cm or larger.⁸ In a recent report from the Central Pancreas consortium spanning 15 years and data on 349 patients from 8 institutions preoperative factors associated with the risk of malignancy were male gender, location at the pancreatic head and neck, increased radiographic size, presence of a solid component or mural nodule and pancreatic duct dilation.⁹ Our patient cohort is different as patients with benign MCNs are not being reported to NCDB and the tumor size reported is routinely pathologic tumor size for resected cases and not radiologic. However, we found a difference of 6.5 years between in situ and invasive adenocarcinoma groups which supports an adenoma to carcinoma model. Interestingly, patients with large tumors could have only in situ disease underlining the importance of radiologic features (mural

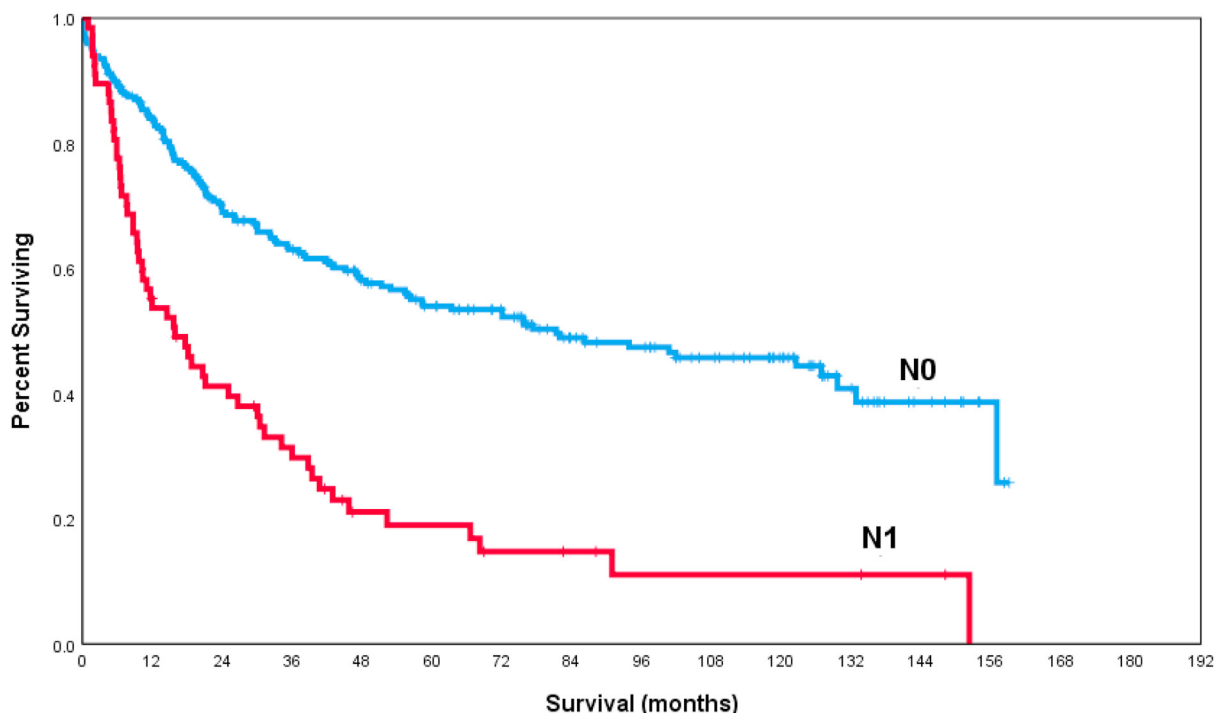


Fig. 2. Survival Outcomes for 315 patients who underwent pancreatectomy for Mucinous Cystic Neoplasm with invasive adenocarcinoma according to lymph node status (node negative disease (N = 248) median OS 81.4months vs 16 months for node positive disease (n = 67); $p < 0.001$).

nodules, pancreatic duct dilation) when evaluating these cysts.⁹

Adenocarcinoma associated with MCNs appears to be distinct and biologically less aggressive compared to pancreatic adenocarcinoma. In the current series lymph node positivity for invasive cancers was only 18.5% and dominated the prognosis whereas 5 year overall survival for invasive disease was 35.4%. These numbers are much more favorable compared to resected pancreatic ductal adenocarcinoma where lymph node positivity occurs in the majority of patients and 5 year survival rates are only around 15%.¹¹ It is likely that some patients with MCNs have indolent disease and can be followed, however at present we do not have the ability to select these patients. The European guidelines suggest the option of surveillance for cysts less than 4 cm without concerning radiologic features.⁷

There are several limitations to this study. National Cancer Database is a population-based database with the highest quality standards on data collection, validation and reporting. However, the possibility of reporting errors is always existent and even with utilization of the specific histologic code for MCNs the possibility that the database includes some IPMNs is real. There are no radiologic data available which is a major determinant in decision making for MCNs. Survival is measured as overall survival rather than disease-specific survival. Despite these weaknesses, NCDB provides a substantial amount of clinicopathologic, oncologic, and treatment data reflecting the nationwide practice patterns in the United States.

Conclusions

In conclusion, the current study utilizing a very large cohort of Mucinous Cystic Neoplasms of the pancreas from the National Cancer Database shows excellent outcomes for adenocarcinoma in situ and 5Y survival of 35.4% for invasive disease with the lymph node status dominating prognosis. Patients with invasive adenocarcinoma were 6.5 years older and more frequently men compared to patients with in situ. Interestingly, the pathologic size between in situ and invasive adenocarcinoma was not different and even large tumors can have only in situ adenocarcinoma.

Sources of support and funding

None.

Declaration of competing interest

To the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

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