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Survival Impact of Malignant Pancreatic Neuroendocrine and Islet Cell Neoplasm Phenotypes

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Abstract

Background—The low incidence of malignant functional (F) or nonfunctional (NF) neuroendocrine islet cell tumors (ICTs) of the pancreas represents a challenge to precise post-therapeutic survival prediction. This study examined the survival impact of malignant pancreatic ICT morphologic subtypes.

Methods—A pancreatic ICT data set was created from a US-based population database from 1980–2004. Prognostic factors with survival impact, and relationships between surgical therapy and overall survival (OS) were analyzed.

Results—There were 2,350 individuals with malignant ICTs. Histologic subtypes included carcinoid tumors, islet cell carcinomas, neuroendocrine carcinomas, and malignant gastrinomas, insulinomas, glucagonomas, or VIPomas. There was no difference in resection rates between FICTs and NFICTs (23% vs. 20%, p=ns). Median OS was 30 months, with group differences ranging from NE carcinomas (21) to VIPomas (96; p<0.0001). Median OS of resected vs. unresected FICTs was 172 vs. 37 months, while that of NFICTs was 113 vs. 18 months (p<0.0001). Compared to neuroendocrine carcinomas, hazard ratios were: VIPomas 0.48, gastrinomas 0.65, carcinoid tumors 0.76, insulinomas 0.84, glucagonomas 0.93, and islet cell carcinomas 1.0.

Conclusions—When controlled for other established prognostic parameters, histopathologic subtype assignment of pancreatic ICTs affects survival prediction. Resection is associated with superior survival for all tumor types.

Keywords

pancreatic neuroendocrine tumor; survival; SEER population data

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Introduction

Pancreatic neuroendocrine islet cell tumors (ICTs) are rare and frequently slowly progressing neoplasms of the pancreas. Distinction between benign and malignant tumors is often only possible through postoperative pathologic examination, or based on the presence of metastases.[1] The annual incidence of ICTs in the U.S. is around 4 to 5 per million, which encompasses <5% of all neoplasms of the pancreas.[2] However, these tumors tend to have a more indolent course and are associated with better survival outcomes compared to pancreatic adenocarcinoma.[3] ICTs arise from the islets of Langerhans and fall into 2 general groups: functional and non-functional. Functional tumors can produce insulin, glucagon, gastrin or vasoactive intestinal peptide, and in case of oversecretion of these hormones, paraneoplastic syndromes can occur. Given the relatively asymptomatic nature of non-functioning ICTs, patients often present with locally advanced or metastatic disease at the time of diagnosis.[1, 4–6] Up to 15 percent of patients have associated MEN1 syndrome, and the prognosis varies widely based on the underlying biologic behavior.[7]

Surgical resection of malignant ICTs has been associated with superior overall survival, even in the face of metastatic disease.[2, 4, 5, 8–14] However, the long-term prognosis of specific histologic ICT subtypes is difficult to predict based on the relative rarity of these tumors. Although tumor grade and stage have consistently shown to be important predictors of survival, the importance of tumor size, histopathologic type, and lymph node status are highly variable, making appropriate staging difficult.[2, 5, 8–11] In patients with small bowel carcinoid tumors, increased tumor cell proliferation associated with elevated Ki67 index is considered a sign of potential aggressive behavior.[15, 16] In addition, elevated plasma chromogranin A levels have been shown to be associated with decreased overall survival. These markers have been suggested for use in nomograms for predicting survival for patients with small bowel carcinoids. However, the use of these markers with universal application to all neuroendocrine tumor variants including pancreatic ICTs has not been established.[16] Recently, the AJCC has incorporated ICTs into the TNM staging criteria previously used for pancreatic adenocarcinoma.[17, 18] However, AJCC-TNM staging does not incorporate tumor grade, which has been consistently shown to be an important predictor of survival.[8, 9, 17, 19] Additional staging systems, including a TNM staging system proposed by the European Neuroendocrine Tumor Society (ENETS) incorporate a proliferative index, but are not universally accepted at this time.[20, 21] Additionally, there have been inconsistent data regarding the importance of functional status, including histopathologic or morphologic tumor subtype as a predictor of survival.[2, 4, 6, 10] To identify the predictive ability of functional status and resection on overall survival requires patient numbers larger than feasible from any single-center surgical series. We thus investigated the relationship between functional status and surgical resection on overall survival of malignant pancreatic ICTs using information from a large US population-based cancer database.

Materials & Methods

A pancreatic cancer data set was created through structured queries to the publicly available version of the Surveillance, Epidemiology, and End Results (SEER) database, covering the

years 1980 to 2004.[22] Due to the paucity of complete data in the SEER database for patients with pancreatic ICTs prior to 1980, patients entered into the SEER database from 1973–1979 were excluded. The SEER program collects clinical information from 20 cancer registries across the United States. From a cohort of 109,596 patients with a diagnosis of pancreatic malignancy, individuals were selected based on the presence of a malignant ICT as identified through the histology diagnostic codes within the SEER data, and based on sufficient clinicopathologic information. Histologic ICT subtypes included islet cell carcinoma, insulinoma, glucagonoma, gastrinoma, vipoma, carcinoid, and neuroendocrine carcinoma. The SEER registries include neuroendocrine neoplasms that are considered invasive or malignant (behavior code 2 or 3 in the International Classification of Disease for Oncology, 3nd edition), [23] but not benign ICTs. Although a tumor, node, metastasis staging system is included in the most recent edition of the American Joint Committee on Cancer, [18] there was no accepted staging system for islet cell carcinoma during the time period studied. Tumors in the SEER registry have been classified as localized, regional or distant; this classification was utilized for stage-related analyses. Detailed information on clinical ICT behavior is not included in SEER data. ICTs with a distinct hormonal profile (insulinomas, gastrinomas, glucagonomas and VIPomas) were classified as “functional” (F) tumors for the sake of group comparisons; all others were considered “nonfunctional” (NF) ICTs.

Group comparisons of categorical data were performed via chi-square testing, and of continuous data through t-test or Mann-Whitney analysis, based on data distribution. The primary outcome parameter of interest was overall survival. Survival time, as tabulated by SEER in monthly increments, was the time from diagnosis until last contact, the date of death, or the date used as a cutoff for the SEER database. Actuarial survival was calculated with the Kaplan-Meier method, [24] and univariate comparison between groups was performed by using the log-rank test. [25] Cox regression served as a multivariate technique, and a backward-elimination model was used for all covariates.[26] The threshold for keeping a variable in the Cox model under backward elimination was $p<0.05$. All calculations were performed using the StatView statistical software package for Macintosh computers (SAS, Cary, NC).

Results

From a cohort of 109,596 patients with carcinomas of the pancreas, 2,350 individuals were identified as having a malignant islet cell or neuroendocrine tumor. The median age was 60 years with a range of 20–95 years. Tumors were more commonly characterized as non-functional (n=2,187) than as functional tumors (n=163, Table 1). Median tumor size was 4.8 cm, with a range of 0.3 – 32.7 cm. Among tumors with a location specified in the database, the majority was located in the head of the pancreas, followed by the tail and body (Table 1). Most tumors were also of low or moderate grade (61% Grade I or II). Sixty percent of patients were classified as having distant disease at the time of presentation. Only 21% of patients underwent a resective surgical procedure, with no difference in resection rates between FICTs and NFICTs (23% vs. 20%, p=ns).

Median OS for the entire patient cohort was 30 months (Figure 1A), with group differences ranging from neuroendocrine carcinomas (21 months) to VIPomas (96 months; p<0.0001; Figure 1B). Patients with low-grade tumors (Grade I or II) demonstrated superior overall survival (OS) compared to patients with high-grade tumors (Grade III or IV; Figure 1C). The presence of distant disease was predictive of inferior survival compared to local or regional disease (Figure 1D). Functional status and resection status had an obvious OS association: median OS of resected vs. unresected FICTs was 172 versus 37 months, while that of NFICTs was 113 vs. 18 months (p<0.0001, Figure 2).

Multivariate OS variables of significance remaining in the final model included age, grade, stage, resection status (p<0.0001), lymph node status information (p=0.0002), histopathologic group (p=0.004), marital status (p=0.0081), and primary tumor site (p=0.03). Tumor size, number of lymph nodes examined, and gender were those variables with a significant OS relationship on univariate analysis, but no significant multivariate impact. Compared to neuroendocrine carcinomas, survival hazards were significantly lower for VIPomas, gastrinomas and carcinoid tumors, but not different in insulinomas, glucagonomas and islet cell carcinomas (Table 2).

Discussion

There are well-established prognostic parameters for survival prediction of malignant pancreatic ICTs, including tumor grade and tumor stage.[2, 4–6, 8, 9, 27] However, the impact of histopathologic subtype and functional status is much less clear. Previous studies attempting to address these questions have been unable to establish a connection between histopathologic subtype and overall survival.[1, 2, 4, 6] Therefore, we analyzed the SEER database to determine the effect of surgical resection, functional status and morphologic tumor type on overall survival, and to identify factors associated with increased risk of death in patients with malignant pancreatic islet cell tumors.

Previous studies have reported numerous factors negatively affecting survival.[2, 4–6, 8, 9, 19] The presence of distant disease has consistently been associated with decreased overall survival.[2, 4, 5, 8, 9] We found that a significant proportion of patients presented with distant disease (60%; Table 1) and that the presence of distant disease was associated with decreased overall survival (Table 2). In this study, increasing age at diagnosis was also associated with decreased overall survival (Table 2). This is consistent with most previous studies.[2, 4, 6, 9] Tumor grade has repeatedly been shown to be one of the most important predictors of overall survival for patients with ICTs and has been incorporated into modifications of the ENETS-TNM and AJCC-TNM staging.[2, 9, 21] In the present study, patients with high-grade (grade III or IV) tumors had significantly decreased survival compared to patients with low-grade tumors.

The effect of marital status on overall survival in cancer patients has been investigated in many types of cancer.[4, 28–30] Although Hill et al. found no association between marital status and survival in patients with ICTs, [4] we identified marital status as a factor with an obvious association to overall survival, as has been the case for various other tumor types for which this information has been available through the SEER database.[31] Data on lymph

node status was only available in 25% of patients. Although there was no difference in survival between patients with known N0 or N+ disease, patients that had data available regarding lymph node status demonstrated superior survival compared to those patients that lacked lymph node staging information. It is assumed that more accurate staging is likely a surrogate for other mechanisms that may influence this effect.

The importance of surgical resection of ICTs on survival has been described in the literature.[4, 5, 9–12, 14] Small series have begun to address the importance of resection of metastatic disease, but data are limited and lack important demographic information including chemotherapy, the use of other regional therapies and the completeness of resections.[10–14, 22] We found similar results in this study, as patients who were able to undergo surgical resection of the primary tumor had significantly longer overall survival compared to patients who did not undergo a resection. This difference in survival outcome was significant in a multivariate analysis with disease extent and tumor size as covariates. Since the resection status is likely influenced by the initial burden of disease, it cannot be concluded from this finding that all patients should undergo resection.

The effect of functional status and tumor type on overall survival has remained unclear and debatable in previous studies. We found that patients with hormonally specifiable tumors classified as functional who underwent resection had better survival compared to patients with resected non-functional tumors, based on a univariate comparison. Additionally, patients with non-functional, unresected tumors had significantly shorter overall survival compared to patients with functional, unresected tumors. Again, this is not a surprise, as “resectable” tumors likely represent earlier stage categories than “unresectable” lesions. It should be kept in mind, however, that strict criteria for the definition of respectability of ICTs do not exist, as tumors with advanced local extent, vascular involvement or metastases may be considered resectable by some and unresectable by others; whether resections carry a significant prognostic benefit in these settings is unproven, but assumed.

In addition to the functional ICT subgrouping, we stratified patient outcome based on histopathologic tumor type. On multivariate analysis, compared to patients diagnosed with neuroendocrine carcinoma, patients with VIPoma had a significantly decreased risk of death. In addition, patients with gastrinomas and those classified as carcinoid tumors displayed a superior survival compared to patients with non-functioning neuroendocrine carcinomas or islet cell carcinomas; interestingly, survival in patients with insulinomas and glucagonomas was not different than that seen for neuroendocrine carcinomas, after controlling for other prognostic factors. Although previous studies have demonstrated a significant survival advantage of functional compared to nonfunctional tumors on survival, [2, 4, 6] these studies have not been able to demonstrate the exact impact of histopathologic subtypes on overall survival, as now demonstrated in the present analysis.

There appears to be a survival disadvantage for patients presenting with MEN1 associated ICTs compared to sporadic tumors. For example, 10-year disease-free survival for patients with sporadic gastrinoma ranges from 30–50% vs. 0% for MEN1 associated gastrinoma.[7] Therefore, the timing and extent of surgical resection for patients with MEN1 associated ICTs is still unclear. Unfortunately, MEN1 status information is unavailable within the

SEER database, which is a limitation of the present study. We assume that some MEN1 patients are included in the cohort analyzed, but are unable to determine the syndrome's impact.

Recently, in addition to the WHO staging system for neuroendocrine tumors, the AJCC and European Neuroendocrine Tumor Society have proposed separate TNM staging systems, with additional modifications of these systems proposed by several other groups. [2, 9, 17, 18, 20, 21, 32] Our study suggests that tumor functional status may be an important prognostic marker, and should be considered in the future development of a universal staging system.

Limitations of SEER database studies should be taken into account when interpreting these results, mainly the lack of reporting or the presence of incomplete data regarding patient comorbidity, other local or regional therapy for metastases, margin status and incomplete resections, and additional systemic therapy including chemotherapy. However, given the relative rarity of these tumors, the number of patients required for a prospective, institution-based study with complete data availability is unlikely to be feasible. Therefore, retrospective studies of large, population-based databases are paramount for a detailed understanding of the biology and natural history of these rare tumor types.

Conclusions

In this study, we have found a clear impact of histopathologic ICT subtype on overall survival, in addition to other, well-established prognostic parameters. Furthermore, we have been able to calculate hazard ratios that can assist in more accurate survival determinations for patients with ICTs. It is anticipated that these findings can serve as useful clinical survival predictors, especially in the setting of resected disease.

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Synopsis

Histopathologic subtype assignment of pancreatic islet cell tumors affects survival prediction. Surgical resection is associated with superior survival for all tumor types.

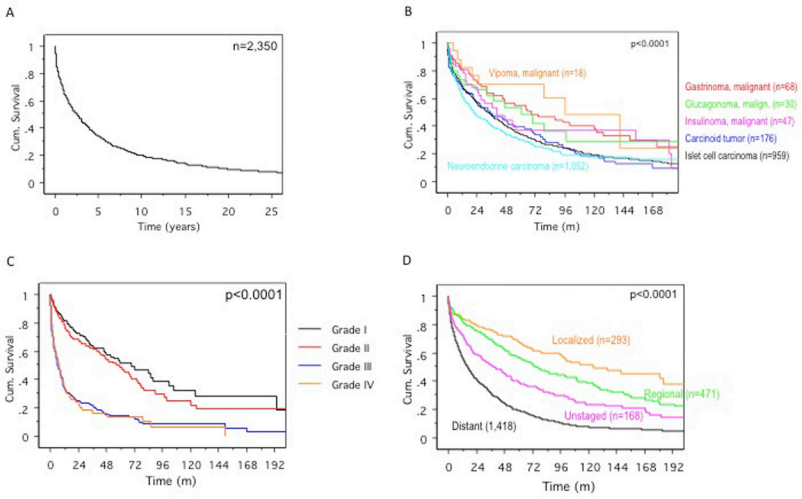

Figure 1. Overall survival

1A: entire patient cohort

1B: by histologic type

1C: by grade

1D: by stage

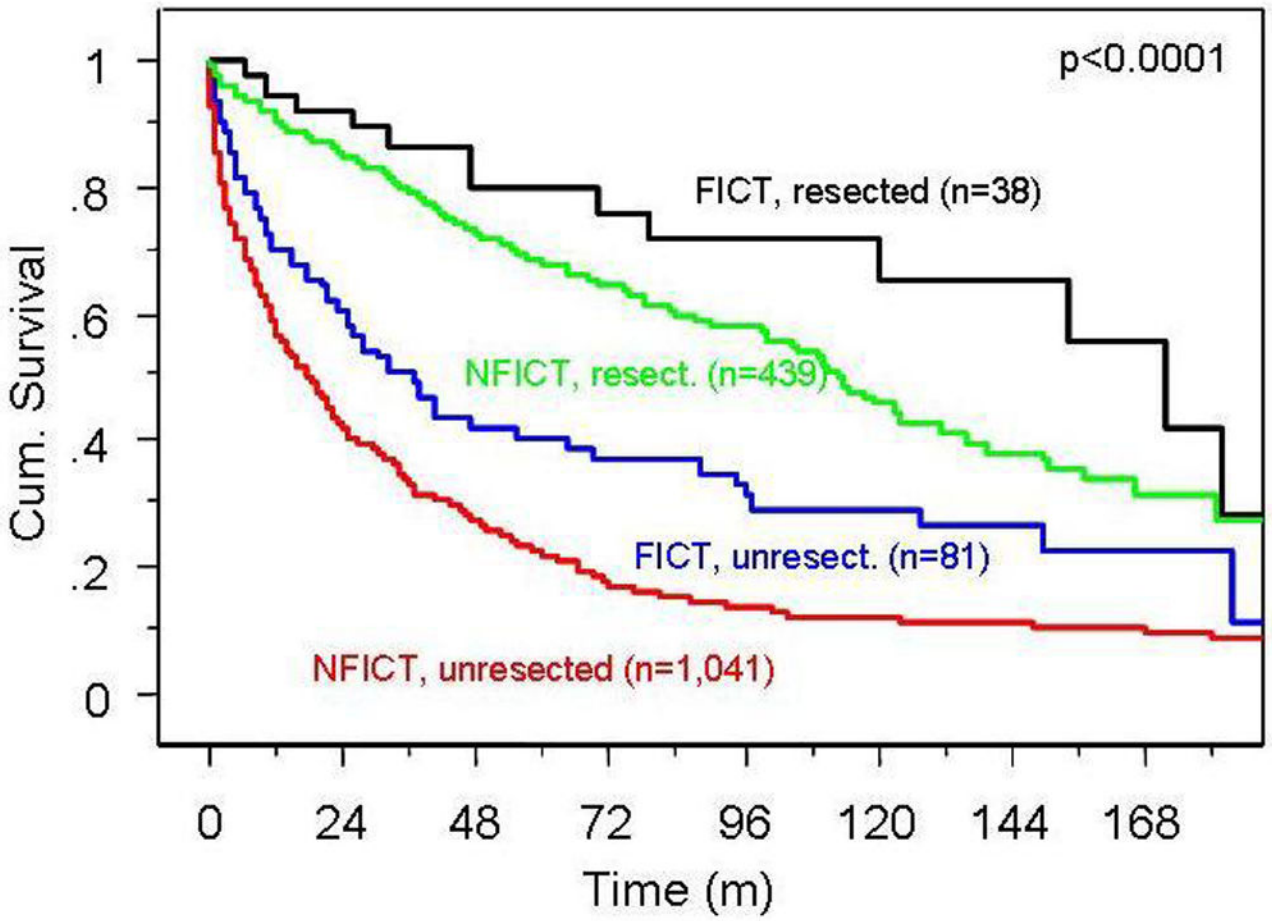

Figure 2.
Overall survival by functional status and resection status

Table 1

Patient, tumor and treatment demographics; n=2,350

Variable		n	%
Gender	Male	1294	55
	Female	1056	45
Marital status	Single	269	11
	Married	1541	66
	Widowed	268	11
	Divorced	210	9
	Unknown	62	3
Race	African-American	224	10
	Hispanic	177	7
	Caucasian	1802	76
	Asian	135	6
	Unknown	12	1
Histopathologic subtype	NE carcinoma	1052	45
	Islet cell carcinoma	959	41
	Carcinoid	176	7
	Gastrinoma	68	3
	Insulinoma	47	2
	Glucagonoma	30	1
	VIPoma	18	1
Primary site	Head	819	35
	Body	222	10
	Tail	517	22
	Unspecified	792	33
Grade	I	218	10
	II	170	7
	III	175	7
	IV	72	3
	Unknown	1715	73
SEER stage	Localized	293	13
	Regional	471	20
	Distant	1418	60
	Unstaged	168	7
Lymph Node Disease	N0	304	13
	N+	262	11
	Unknown	1784	76
Resection Status	Resection	489	21
	Unresected	1110	47

Variable		n	%
	Other nonresective procedure	485	21
	Unknown	266	11
Radiation	Yes	188	8
	No	2124	90
	Unknown	38	2

Table 2

Cox proportional hazard analyses of potential prognostic factors

Covariate	Univariate p-value	Multivariate p-value	Subgroups	HR (95% CI)	p-value
Resection status	<0.0001	<0.0001	Resection	.43 (.35–.53)	<0.0001
			Unresected	.86 (.75–.99)	<0.0001
			Unknown	1.0 (ref.)	
Stage group	<0.0001	<0.0001	Localized	.82 (.62–1.09)	0.17
			Regional	.97 (.76–1.23)	0.77
			Distant	1.67 (1.36–2.03)	<0.0001
			Unspecified	1.0 (ref.)	
Grade	<0.0001	<0.0001	I	.79 (.62–.99)	0.45
			II	.84 (.67–1.1)	0.12
			III	2.09 (1.75–2.52)	<0.0001
			IV	2.13 (1.63–2.79)	<0.0001
			Unspecified	1.0 (ref.)	
Age	<0.0001	<0.0001		1.027 (1.02–1.03)	<0.0001
Lymph node status	<0.0001	0.0002	N0	.69 (.53–.89)	0.0059
			N+	.64 (.51–.81)	0.0002
			Unknown	1.0 (ref.)	
Histopathologic type	<0.0001	0.0037	VIPoma	.48 (.24–.97)	0.04
			Gastrinoma	.65 (.47–.90)	0.0086
			Carcinoid	.76 (.61–.93)	0.0084
			Insulinoma	.84 (.56–1.26)	0.40
			Glucagonoma	.93 (.57–1.51)	0.77
			NE carcinoma	1.0 (ref.)	
			Islet Cell Carcinoma	1.01 (.90–1.14)	0.86
Marital status	<0.0001	0.0081	Single	1.05 (.85–1.31)	0.64
			Married	.91 (.78–1.07)	0.27
			Widowed	1.0 (ref.)	
			Divorced	1.22 (.98–1.54)	0.08

Covariate	Univariate p-value	Multivariate p-value	Subgroups	HR (95% CI)	p-value
Primary Site	<0.0001	0.0318	Head	1.06 (.92–1.23)	0.41
			Body	.94 (.76–1.16)	0.56
			Tail	1.0 (ref.)	
			Unspecified	1.19 (1.03–1.37)	0.0207